Dosage—Pyridium is usually administered orally in doses of 0.2 Gm (3 grains) three times daily either as powder in capsules or as tablets, for local application to wounds, ulcers and infected surfaces an aqueous solution of 0 5 to 1 per cent may be used, for urethral injection a 0 3 per cent solution is used

Pyridium should not be used in connection with compounds containing mercury as it releases the mercury from such compounds It is contraindicated in uremia and in severe disorders of the kidneys of a noninfectious type.

Pyridium is only slightly soluble in cold water about 1 part in 300 However it will form supersaturated solutions relatively easily Pyridium will precipitate out of a 2 per cent (supersaturated) solution after approximately two days it will precipitate out of a 1 per cent solution only after months A 1 per cent solution may be stabilized for months by the addition of 10 per cent dextrose U S P X Aqueous solutions should be prepared with distilled water as the salts present in the tap water of many localities are liable to precipitate the free base, phenylazo α-α-diamino pyridine

Manufactured by the Pyridium Corporation of New York (Merck & Co Inc. distributor) U S patents 1 680 108 (Aug 7 1928 expires 1945) 1 680 109 (Aug 7 1928 expires 1945) U S trademark 251 253

Aqueous Solution of Pyridium 1 per cent Pyridium 1 Gm anhydrous dextrose 10 Gm distilled water to make 100 cc This is a super saturated solution any deposit appearing may be redissolved by warming

Pyridium Ointment 10 per cent Pyridium 10 per cent wool fat 77 5 per cent expressed oil of almond 12 5 per cent.

Pyridium Tablets 0 1 Gm

Pyridium occurs as a red odorless microcrystalline powder possessing a slightly bitter taste slightly soluble in cold water about 0 3 part in 100 parts soluble in boiling water about 5 parts in 100 parts slightly soluble in alcohol soluble in glacial acetic acid insoluble in acetone benzene chloroform ether and toluene although these solvents might be colored slightly yellow by its presence if the solvents are not entirely free from water the aqueous solution (1 in 500) is red and is distinctly acid in reaction when measured by means of the hydrogen electrode On addition of diluted sulphuric acid or a dilute solution of sulphates to an aqueous solution of pyridium a precipitate forms

Digest about 0 2 Gm of pyridium with 10 cc. of diluted hydrochloric acid for thirty minutes at 50 C the dihydrochloride separates as small dark red crystals or scales decant the supernatant liquid and add 20 cc. of water to the crystalline precipitate the material dissolves Dissolve about 0 5 Gm of pyridium in 500 cc of water add an excess of ammonia water collect the resultant free base phenylazo-alpha alpha diamino pyridine on a filter paper wash recrystallize from water and dry at 100 C it melts at 137 to 139 C

Dry about 1 Gm of pyridium accurately weighed to constant weight over sulphuric acid in a partial vacuum the loss in weight does not exceed 1 per cent Incinerate about 1 Gm accurately weighed previously dried over sulphuric acid the ash does not exceed 0 3 per cent Dissolve about 1 Gm of pyridium accurately weighed previously dried over sulphuric acid in 200 cc. of warm water collect the insoluble matter if any in a weighed Gooch crucible wash the insoluble matter with hot water dry and weigh the residue at 100 C the insoluble matter does not exceed 0 5 per cent The nitrogen content determined according to the Dumas method in Clarke s Handbook of Organic Analysis ed 2 p 199 the nitrogen is not less than 28 0 per cent nor more than 29 3 per cent when calculated to the dried substance Transfer about 0 5 Gm of pyridium accurately weighed to a 600 cc. beaker and dissolve in 250 cc. of water previously boiled to remove carbon dioxide the hydrogen chloride content determined by titration with tenth normal sodium hydroxide solution using the hydrogen electrode and a calomel cell (normal potassium chloride solution) corresponds to not less than 14 5 per cent nor more than 15 per cent of hydrogen chloride when calculated to the dried substance

POLLEN ANTIGENS-NATIONAL—Liquids obtained by extracting the dried pollen of plants with a 0 5 per cent sodium chloride solution containing approximately 0.28 per cent of sodium bicarbonate and 0 4 per cent of phenol

Actions and Uses—See Allergic Protein Preparations New and Nonofficial Remedies 1930 p 23

Dosage—See Allergic Protein Preparations, New and Nonofficial Remedies, 1930 p 23

Pollen Antigens-National are marketed in packages of one 5 cc vial containing 50 units per cubic centimeter in packages of one 5 cc. vial containing 100 units per cubic centimeter and in packages of one 5 cc. vial containing 250 units per cubic centimeter

Manufactured by the National Drug Co Philadelphia No U S patent or trademark

Ragweed Pollen Antigen National (Ambrosia elatior and Ambrosia trifida) Timothy Pollen Antigen National (Phleum pratense)

Pollen antigens National are prepared by the following method the pollen is weighed and extracted with ether After removal of the ether the pollen is mixed with the extracting liquid consisting of a 0 5 per cent sodium chloride solution containing approximately 0.28 per cent of sodium bicarbonate and 0 4 per cent of phenol and then covered with toluene. After four days during which time the mixture is shaken once or twice daily the supernatant fluid is decanted and the sediment mixed with a second portion of extracting fluid As soon as the sediment has settled the supernatant fluid is decanted and mixed with the first portion The combined decanted fluid is then subjected to Berkefeld filtration Each cubic centimeter of the finished liquid represents the extractives of 0 01 Gm. of pollen The unit is that established by Noon approximating 0 001 mg of protein nitrogen

REPORTS OF THE COUNCIL

The Council has authorized publication of the following report W A Puckner Secretary

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POMPEIAN OLIVE OIL NOT ACCEPTABLE FOR N N R

Pompeian Olive Oil was presented by the Pompeian Corporation Baltimore, with the request that it be considered by the Council for inclusion in New and Nonofficial Remedies The firm presented details to show the care taken and the chemical control exercised to insure a high grade product, and the product might be recognized as a brand of olive oil U S P., marketed under the pharmacopeial name (Pompeian' being used merely to identify the firm s brand), were it not that claims of unique advantage and therapeutic potency are advanced The Council cannot admit in reference to this brand of oil the claim made that the ease of its digestion and assimilation is far greater than that of any other vegetable or animal oil" Claims of medicinal value based on such a composition are unwarranted.

The firm was informed that the Council would find no objection to this product s being advertised as a high grade olive oil under conditions that would make it acceptable as a nonmedicinal food that the admitted therapeutic uses apply to other fats and do not constitute an occasion for special consideration, that this oil if presented without claims of special therapeutic value but simply as a pharmacopeial product might be considered for exemption under the Council s rules and that Pompeian Olive Oil as presented, is unacceptable for New and Nonofficial Remedies The firm replied, agreeing that in view of the lack of evidence to substantiate the claims presented such claims are considered unwarranted and presented a preliminary report by Dr Walter H Eddy submitting evidence to show that Pompeian Olive Oil contained vitamin A in appreciable amount, while vitamin B was not detected with a report by Dr Maynard Ladd on the feeding of infants with Pompeian Olive Oil homogenized with fat free certified milk in amounts to give approximately 3 5 per cent of fat in the homogenized mixture He concludes I think we may infer that virgin olive oil of the quality which we used which was furnished by your company when freshly homogenized with certified fat free milk, serves at least equally well with certified cow s milk in the nutrition and development of infants in the first year In place of the originally submitted information the firm submitted a revised description of Pompeian Olive Oil The statement under Pharmacologic Action reasserts in effect the claim based on ease of assimilation and concludes No attempt will be made at this point to recite the medicinal properties of POMPEIAN Olive Oil that arise from its Vitamin A content The many readily available references to the value of the growth-promoting or antixerophthalmic vitamin should obviate further explanation'

The evidence submitted by Dr Eddy regarding the vitamin A content of Pompeian Olive Oil and the report of Dr Ladd s tests are gratifying and worthy of note Further evidence, besides the Eddy report however is needed to show that the vitamin A content of the product differs constantly from that of other brands The Ladd report also requires further confirmation Even if confirmed however and considering further the firm s somewhat modified claims these reports do not constitute an occasion to give this brand of olive oil a place in New and Nonofficial Remedies Olive oil is a well known food It doubtless has some dietotherapeutic indications but these are akin to those of butter fat and cream neither of which would be regarded by the Council as a medicinal food in the sense defined by it. The brand does not have any unique vitamin content such as justifies the inclusion of assayed cod liver oil in N N R The uniqueness of the Pompeian oil lies in the demonstration that it actually contains some vitamin in contrast with many other commercial edible oils The Council voted to affirm its decision that Pompeian Olive Oil is unacceptable for New and Nonofficial Remedies

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ERYSIPELAS

A COMPARATIVE STUDY OF THE MORE RECENT METHODS OF TREATMENT *

WALTER H UDE, MD
AND
E S PLATOU, MD
MINNEAPOLIS

Dissatisfaction with the results obtained by topical applications in the treatment of erysipelas has led to the investigation of various other methods Three of these may be considered of major importance, namely, (1) roentgen irradiation, (2) ultraviolet irradiation, (3) intramuscular injection of a specific antitoxin We have used these methods to a considerable extent We were at first favorably impressed with the effects of roentgen irradiation Certain disadvantages, such as the inherent dangers, the expense, the lack of proper facilities in all communities, and the necessity that this form of treatment be given under the supervision of a trained radiologist, have induced us to try to find other methods The use of antitoxin has certain disadvantages such as the expense, the necessity for repeated injections, and the dangers of sensitization and serum reactions Ultraviolet irradiation has none of the objectionable features of the other methods, while it seems to excel them in effectiveness We are now using ultraviolet radiation in all of our cases of erysipelas

Since the publication of the work of Platou and Rigler,[1] in 1926 there has been only one additional report on the effects of roentgen therapy in erysipelas, that by Harbinson and Lawson[2] They treated eleven cases, using unfiltered radiation and a smaller dose than that advocated by Platou and Rigler, but with about the same results Their dose is small enough so that it can be easily repeated without danger This method has also been used by Leddy and Ford[3] of the Mayo Clinic They report good results in most cases but find that unfiltered radiation and small doses produce much the same results as the larger filtered doses They have found some of their postoperative cases very retractable

There has been little recent work published on the use of ultraviolet irradiation in erysipelas and no reports except our own[4] are available in instances in which it has been used in an extensive series of cases Becker[5] in Germany gives one and one-half skin erythema doses, leaving a wide margin about the area involved The youngest patient treated and cured by him was 5 months old Sampson,[6] in his textbook is an enthusiastic advocate of this method His technic of application and our own correspond closely Stewart[7] also refers to this method as beneficial, but he does not seem to have had any extensive experience with the disease Ide and his co-workers[8] at the Northern Pacific Hospital in St Paul have employed the method for several years and were the first to call it to our attention Their results are comparable to our own

In the present discussion we are stressing the comparative results of roentgen and ultraviolet irradiation in erysipelas We have made a comprehensive analysis of all the available data in 402 hospitalized cases These have been classified according to the method of treatment employed, and the data have been so arranged that a fairly accurate comparison of the results can be made All cases treated by the various methods were studied, with the exception of only a few in which the erysipelas was a complicating factor of other diseases from which the erysipelas picture could not be separated and in which the primary disease predominated the clinical course We are omitting in this presentation a discussion of the clinical progress of the disease under the various forms of therapy, as this has been covered in previous publications

Our group of controls comprises all the cases of erysipelas treated in the department of contagious diseases of the Minneapolis General Hospital during the years 1922, 1923 and 1925 We omitted the cases for 1924, as this was the year of the smallpox epidemic This disease not only limited the number of admissions of patients with other conditions to the contagious wards but also was frequently complicated by erysipelas Statistics on the 1924 cases are therefore difficult to analyze, and we thought that they had best be omitted Our control cases were treated with magnesium sulphate and glycerin packs to the local lesions, other treatment being symptomatic

The cases included in our series treated by roentgen irradiation are the hospitalized cases of the group previously reported by Platou and Rigler[1] The technic has also been reported in detail We used light filtration (2 mm aluminum) and closely approached the mild skin erythema dose A sufficient margin of normal skin was allowed, and several areas were exposed in order to reach the entire region involved We are under the impression that a fairly large dose

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* From the departments of roentgenology of the Minneapolis General Hospital and the University of Minnesota and the department of contagious diseases of the Minneapolis General Hospital

1 Platou, E S and Rigler Leo Roentgen Ray Therapy in Erysipelas Arch. Int. Med. **38** 573 (Nov) 1926

2 Harbinson J E and Lawson J D The Treatment of Erysipelas by Roentgen Ray California & West. Med. **26** 485-487 (April) 1927

3 Leddy E T and Ford Frances *Personal communication to the authors*

4 Ude W H Ultraviolet Radiation Therapy in Erysipelas Radiology **13**: 504 (Dec.) 1929

5 Becker J München. med. Wchnschr **74** 497 (March 25) 1927

6 Sampson C M Practice of Physiotherapy 1926

7 Stewart H E Physiotherapy 1926

8 Ide A W et al Personal communication to the authors

is needed to produce the desired results The hair was carefully protected from excessive exposure, and, when the scalp was involved, lighter dosages were used The eyes and eyebrows were protected

The cases included in our series treated by ultraviolet irradiation were all hospitalized We did not include any of the ambulatory cases or any of those treated in private practice, as we could not fit the data on these into a hospitalized series For this type of treatment we use the quartz mercury vapor lamp The burner is placed at 8 inches distance from the patient in order to get as large a concentration of the short wavelengths as possible The exposure time varies with the efficiency of the lamp and is approximately twice the time required to produce a mild erythema on normal skin This dose is below the vesiculating dose but produces a strong erythema As the general efficiency of the lamp decreases with age, the exposure time must be increased With a new burner we used four minutes as our exposure time, and now, with considerable deterioration of the burner, the time has been increased to ten or twelve minutes per area in order to secure the same therapeutic results In infants or children we make allowance for the increased sensitivity of the skin by a smaller dosage The eyeballs are carefully protected by black paper, but the eyebrows are not covered A margin of one inch of normal skin beyond the raised edge of the diseased area is included in the field If the scalp is involved, no attempt is made to protect any part of it If the entire involved area is easily covered by one exposure, this completes the treatment In bilateral facial involvement or in other locations in which one exposure will not reach well beyond the margins, two or three areas are exposed and these are permitted to overlap The treatment is occasionally repeated two days later, and there is no contraindication to further repetition However, we do not repeat the treatment unless there is definite extension Local applications of magnesium sulphate solution or other substances are not necessary following irradiation, although they may be used for their soothing effect All other treatment is symptomatic We feel that the important factor in this method is a correct application of the technic at the time of the first treatment A preliminary report on this method has recently been made by one of us[4]

In our cases treated with erysipelas antitoxin, Lederle's or Squibb's products were used We have not used the intravenous method, all injections having been made intramuscularly Repeated dosages were given when necessary

COMPARATIVE STUDIES

In our studies, we are placing major importance on the comparison of the following factors (*a*) duration in days from treatment to absolutely normal temperature, (*b*) average time to normal symptoms; (*c*) average duration of the disease from treatment to the day of discharge from the contagious disease hospital, (*d*) average entire duration of the disease, namely, from onset to the day of discharge from the hospital, (*e*) extension of the disease after treatment

In studying the temperature charts, one is tempted to take as the end-point the critical drop in temperature that usually takes place within the first forty-eight hours However, we thought it safer to record the time at which there was no elevation of the temperature above the normal at any time during the day or any subsequent days, so that we could feel that there was no further toxic absorption From this comparison of temperatures we excluded all cases in which the course was afebrile, as well as those that ended fatally

The average time until the symptoms become normal would ordinarily denote the cure of the condition However, it is a regulation of our department of contagious diseases to detain all patients with erysipelas for at least four days after a return to normal temperature This factor is no doubt responsible for the wide variation between the average figure and the duration from treatment to discharge from the hospital

Table 1—*Comparative Study of Therapy in Four Hundred and Two Cases of Erysipelas*

	Method of Therapy					
	Magnesium Sulphate and Glycerin Pack	Roentgen Irradiation	Ultraviolet Irradiation	Antitoxin	Roentgen Irradiation and Antitoxin	Ultraviolet Irradiation and Antitoxin
When treated	1922, 1923 1925	1/22/26 to 9/25/28	10/2/28 to 9/1/29	1/1/27 to 4/30/29	1/22/26 to 9/25/28	10/2/28 to 9/1/29
Number of cases treated	151	113	79	12*	26	21
Number and percentage of deaths	30 or 19.9%	15 or 13.3%	6 or 7.6%	0	4 or 15.4%	5 or 23.8%
Number and percentage of deaths due directly to erysipelas	27 or 17.88%	14 or 12.4%	5 or 6.3%	0	4 or 15.4%	5 or 23.8%
Number of recoveries	121	98	73	12	22	16
Average time to normal temperature	6.15 days	3.8 days	3.16 days	4.46 days	5.92 days	4.00 days
Average time to normal symptoms	8.65 days	5.32 days	4.5 days	5.46 days	7.37 days	6.41 days
Extensions after treatment		29 or 25.8%	6 or 7.6%	2 or 18.2%	11 or 45.8%	3 or 14%
Average duration from treatment to discharge	11.53 days	8.03 days	6.2 days	9.42 days	12.60 days	11.82 days
Average duration from onset to discharge..	14.46 days	12.15 days	10.4 days	11.67 days	17.83 days	16.41 days
Number of patients less than 1 year of age	10	7	3	0	2	4
Percentage of deaths among patients less than 1 year of age	70%	85.7%	33⅓%	0	50%	50%

* All of these were mild cases

Table 2—*Comparative Study of Therapy in Uncomplicated Cases of Erysipelas*

	Method of Therapy				
	Roentgen Irradiation	Ultraviolet Irradiation	Serum	Roentgen Irradiation and Serum	Ultraviolet Irradiation and Serum
Number of cases treated	87	68	10	20	12
When treated	1/22/26 to 9/25/28	10/2/28 to 9/1/29	1/1/27 to 4/30/29	1/22/26 to 9/25/28	10/2/28 to 9/1/29
Average time to normal temperature	3.39 days	3.46 days	4.73 days	5.15 days	3.58 days
Average time to normal symptoms	5.06 days	4.44 days	5.36 days	6.45 days	5.07 days
Average duration from treatment to discharge	7.5 days	7.83 days	7.04 days	10.0 days	8.92 days
Average duration from onset to discharge	10.87 days	10.24 days	9.73 days	15.25 days	14.25 days

Table 1 includes all of our cases of erysipelas from January, 1922, to September, 1929, except the 1924 series One hundred and fifty-one cases were treated with magnesium sulphate and glycerin packs, 113 with roentgen radiation, 79 with ultraviolet radiation, 12 with antitoxin, 26 with combined roentgen radiation and antitoxin, and 21 with combined ultraviolet radiation and antitoxin As the cases treated by both radiation and antitoxin were selected from the same groups as those treated by radiation alone, the criticism may be made that these comprise the more severe cases and thus are not representative, and also that the segregation of these smaller groups improves the statistical study in the larger groups The first criticism may be met by the results shown in table 2, in which only uncomplicated cases are compared and in which the final average results are only slightly altered The second criticism applies to a limited extent, as may be ascertained by combining the smaller groups with the groups treated only by irradiation By doing this the average figures of the irradiated groups are only slightly affected, so that the general conclusions drawn from the study need not be materially altered

A careful study of table 1 will reveal a definite advantage for the more recent methods of treatment, including roentgen irradiation, ultraviolet irradiation, and antitoxin, and will show that the best average results were obtained with ultraviolet irradiation None of our methods seem to produce the striking results obtained by Birkhaug,[9] Symmers and Lewis,[10] and Symmers[11] with the use of antitoxin We do not know how to explain this, as in our hands the use of antitoxin in even the mildest cases does not improve our statistics Our patients, however, appear to return to normal, or are actually cured, in approximately the same average time as Symmers' "average number of days in the hospital of all patients treated with antitoxin" We feel that we may therefore assume that our statistics show longer hospitalization because of more prolonged observation in our contagious disease wards, and that aside from this our results compare favorably with those of the authors named

These more recent methods of treatment have produced a reduction of 40 per cent in the mortality rate when compared with the series treated by magnesium sulphate packs If we eliminate those cases in which death was due to other causes and in which the erysipelas was not the direct cause of death, we find a reduction of 44 per cent in the mortality Comparison of the individual methods of therapy shows the lowest mortality rate in the ultraviolet series

The temperature charts show a return to normal temperature from two and one-half to three days sooner in the cases treated by radiation than in those treated by the older method A return to normal symptoms took place three or four days sooner in the irradiated group In these figures the ultraviolet group also shows distinctly better results than any of the other groups

We attempted to determine the number of cases that showed extension of the local lesion after treatment This could not be determined in our control cases as the clinical notes were incomplete In the later groups this could be determined The roentgen irradiation group showed extension of the disease in 25 8 per cent, while the ultraviolet irradiation group showed 7 6 per cent extension This rather marked variation may to some extent be due to the fact that the erythema following the latter method of treatment has a tendency to overshadow the local evidences of the disease However, it shows that in 92 per cent of the ultraviolet series the disease is clinically arrested by the first treatment

Probably the most critical test to which these methods of treatment may be subjected is a comparison of their effect on the total duration of the disease, and the duration of the disease after institution of the treatment Our average results in this comparison show that the duration of the disease after roentgen irradiation averages two and one-third days less than in the control cases, while the ultraviolet series shows a corresponding advantage of three and one-third days The total duration of the disease has been shortened by four days in the ultraviolet series, while the roentgen irradiation series shows a reduction of only 2 31 days Our small group of cases treated only by antitoxin here compares favorably with the ultraviolet series Although we do not presume to be able to draw final conclusions on such a small series of cases, we feel that there is no advantage in the use of antitoxin as compared with the use of ultraviolet radiation This is especially evident when we consider that the group of twelve cases treated by antitoxin comprised the mildest cases in which we felt that we could experiment with this method of treatment In fact, the forty-seven patients given the combined treatment of roentgen irradiation and antitoxin and ultraviolet irradiation and antitoxin usually received antitoxin as the initial treatment, and were irradiated only when it became evident that they did not respond The statistics of these two groups compare very unfavorably with those of the control series, and with those of the irradiated groups In table 2, in which we eliminate all of the complicated cases and quote the average statistics for the uncomplicated cases only, we substantiate the impression that a combination of irradiation and antitoxin has no advantage over the older method of treatment by magnesium sulphate packs

The mortality rate in infants has always been high In our group of twenty-six cases it is 65 4 per cent Although the rate for the ultraviolet group of seven cases is below this average, we do not presume to lay much emphasis on this fact as the group is entirely too small for any deductions

Table 2 shows a comparative study of the data in uncomplicated cases in which only one type of therapy was given, and includes under separate classification the uncomplicated cases in which combined irradiation and antitoxin therapy was given This table merely substantiates the conclusion drawn from table 1 namely, that in our hands either form of irradiation produces approximately the same results as antitoxin therapy

SUMMARY

1 We have made a comprehensive analysis of all the available data in 402 hospitalized cases of erysipelas These were classified according to the method of treatment, and the data have been so arranged that a fairly accurate comparison of the results can be made

2 The methods of treatment in these cases were as follows (*a*) magnesium sulphate and glycerin packs (*b*) roentgen irradiation, (*c*) ultraviolet irradiation (*d*) erysipelas antitoxin (*e*) roentgen irradiation and antitoxin, (*f*) ultraviolet irradiation and antitoxin

3 The newer methods of treatment have reduced the mortality rate of erysipelas approximately 44 per cent

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[9] Birkhaug K. E. Erysipelas J A M A. 86 1411 (May 8) 1926

[10] Symmers Douglas and Lewis K. M Antitoxin Treatment of Erysipelas J A M A 89: 880 (Sept. 10) 1927

[11] Symmers Douglas The Antitoxin Treatment of Erysipelas J A. M A 91 535 (Aug 25) 1928

4 In cases treated by either roentgen or ultraviolet irradiation, the immediate results are exceedingly gratifying The return to normal temperature and absence of symptoms takes place from three to four days earlier than in cases treated by the magnesium sulphate and glycerin pack method

5 Ultraviolet irradiation produced a clinical arrest of the disease with the first treatment in 92 per cent of our cases

6 Irradiation and antitoxin therapy definitely reduce the total duration of the disease as well as the average duration of the disease after the institution of treatment, and here also ultraviolet irradiation appears to give the best average results

7 On the basis of this study we conclude that the newer methods of treatment show distinct advantages over the older methods, that the results obtained by either form of irradiation and by antitoxin are approximately the same, with slightly more favorable results in the ultraviolet group

8 We further conclude on the basis of our clinical experience with the newer methods of therapy as well as on the basis of the present study that the treatment of erysipelas by ultraviolet irradiation may be advocated as a universally applicable method (*a*) it is readily available in practically all communities and is devoid of danger, as contrasted with roentgen irradiation and antitoxin, (*b*) it usually requires only one treatment, but the treatment may be repeated several times without the least danger, (*c*) it is inexpensive, (*d*) the results are somewhat better in our hands than those of any other method of therapy

701 LaSalle Building—951 Medical Arts Building

MEASLES PROPHYLAXIS

COMPARATIVE RESULTS WITH THE USE OF ADULT BLOOD CONVALESCENT SERUM AND IMMUNE GOAT SERUM (TUNNICLIFF)*

L. H BARENBERG M D
J M LEWIS M D
AND
W H MESSER M D
NEW YORK

The high morbidity and mortality associated with measles in infants and young children, particularly those housed in institutions, urges the use of a procedure that will either prevent or modify this disease To accomplish this end, Nicolle and Conseil,[1] in 1918 recommended the serum of patients convalescing from measles It is now well established that convalescent measles serum is very effective in preventing measles when given in sufficient dosage in the course of the first five days of the incubation period and in attenuating the disease when given either in smaller amounts or somewhat later in the incubation period In spite of its great clinical value, however, convalescent measles serum has not come into general use, chiefly because of the difficulty encountered in procuring it Cases of measles in adults are uncommon, and in the case of children the parents are reluctant to allow blood to be withdrawn, especially during convalescence For this reason investigators have been striving, during the past few years, to find another antimeasles agent that is available and at the same time effective

The permanent immunity that almost invariably follows one attack of measles and the fact that a mother who has had measles imparts to her offspring sufficient antibodies to render the infant immune for the first few months of life indicate that most adults have an appreciable amount of these immune bodies in their blood It was therefore logical that the value of adult blood in the prophylaxis of measles should be investigated In 1920 Degkwitz [2] inoculated "adult serum" into seven children who had been exposed to measles, six receiving 30 cc and one 20 cc of serum Four of the seven developed measles, but in an attenuated form One year later, Rietschel [3] reported good results from the use of adult blood During an outbreak of measles that occurred in an asylum harboring children from 1 to 2 years of age, Rietschel injected 20 cc of adult whole blood into three exposed children and five served as controls The three treated children came down with a markedly attenuated form of measles, whereas the five who remained untreated developed typical measles complicated by bronchopneumonia in two instances Later, Salomon,[4] Gerlach,[5] Hilsinger,[6] Kovacs [7] and others abroad and Zingher,[8] Karelitz and Levin,[9] Bivings,[10] Bader [11] and Van Cleve [12] in this country reported favorable results with the use of adult whole blood or serum as a prophylactic measure against measles

Within the past decade or so, several investigators have isolated from patients with measles various organisms to which they attached etiologic significance Tunnicliff [13] isolated a gram-positive green-producing diplococcus from the nose, throat and blood in early cases Some years later, Ferry and Fisher [14] isolated a gram-positive streptococcus in patients having measles and designated this organism *Streptococcus morbilli* Degkwitz [15] also has described an organism which he considered the causative agent of measles All the investigators injected their organisms into either goats or horses with the purpose of producing an effective antimeasles serum The reports of the clinical value of these serums have not been at all uniform The most favorable and consistent results, however, seem to have been obtained with the use of immune goat serum (Tunnicliff) Thus, in 1926 Hoyne and Gasul [16] reported that, of thirty-nine children exposed to measles and given Tunnicliff serum, thirty-four remained free from the disease and five developed an attenuated form of measles Of the nine children who did not receive the serum, eight came down with typical measles, two of whom died Tunnicliff and Hoyne[17] published their experiences with the use of immune goat serum in sixty persons who had been exposed to measles When the serum was given during the first three days of the incubation period, the disease was prevented in 97 per cent of the cases, but when given later than the fourth day no protection occurred In 1928 Peterman[18] reported that complete protection resulted in thirty-one of thirty-four exposed children who were inoculated with Tunnicliff serum Reports of favorable results have been published also by Halpern,[19] Hoyne and Peacock,[20] and recently again by Peterman[21]

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* From the Home for Hebrew Infants service of Dr Alfred F Hess.

[1] Nicolle C. and Conseil E. Bull. et mém. Soc med. d. hop de Paris **42** 336 1918

[2] Degkwitz R. Ueber Masern Rekonvaleszentenserum Ztschr f Kinderh **27** 171 1920

[3] Reitschel Zur Masernprophylaxe nach Degkwitz Ztschr f Kinderh **29** 127 1921

[4] Salomon G Die prophylaktische Injektion von Normalserum als Masernschutz Deutsche med. Wchnschr **49** 1151 (Aug 31) 1923

[5] Gerlach H Ueber prophylaktische Schutzimpfung mit defibriniertem Erwachsenen Blut bei Masern Monatschr f. Kinderh. **28** 236 (June) 1934

[6] Hilsinger W Erwachsenblut Einspritzungen zum Masernschutz Arch f Kinderh **76** 211 (Aug) 1925

[7] Kovacs E Erfahrungen mit der Rietschelschen Masernprophylaxe Deutsche med Wchnschr **51** 1703 (Oct. 9) 1925

[8] Zingher Abraham Convalescent Whole Blood Plasma and Serum in Prophylaxis of Measles J A M A. **82**: 1180 (April 12) 1924

[9] Karelitz Samuel and Levin Samuel Measles Prophylaxis by Use of Convalescent Serum Adult Blood or Serum Am. J Dis Child **33** 408 (March) 1927

[10] Bivings L Measles Prophylaxis by the Use of Parents Blood Serum South M J **20** 735 (Sept) 1927 abstr J A M A **89** 1724 (Nov 12) 1927

[11] Bader G B The Intramuscular Injection of Adult Whole Blood as Prophylactic Against Measles, J A M A **93** 668 (Aug 31) 1929

[12] Van Cleve J D Measles Prophylaxis with Serum of Adults Who Had Measles in Childhood Arch Pediat. **47** 124 (Feb) 1930

[13] Tunnicliff Ruth The Cultivation of a Micrococcus from Blood in Preeruptive and Eruptive Stages J A M A **68** 1028 (April 7) 1917

[14] Ferry N S and Fisher L. W Measles Toxin J A. M A. **86** 932 (March 27) 1926

[15] Degkwitz R Spezifisches Masernschutzserum vom Tier Munchen med Wchnschr **73** 181 (Jan 29) 1926

[16] Hoyne, A. L. and Gasul B M Measles Prophylaxis Report on the Use of Immune Goat Serum J A M A **87** 1185 (Oct 9) 1926

An epidemic of measles broke out in the Home for Hebrew Infants in the spring of 1929 and lasted two months This institution harbors approximately 325 children, about 150 being under 2 years and the remainder from 2 to 4 years of age During the past fifteen years, several outbreaks have occurred in this institution and there is no contagious disease for which we have greater fear The death rate in the institution has been highest during those years in which measles has occurred, the increase in mortality having resulted from complicating pneumonia and empyema It was therefore of the greatest urgency to check the epidemic as quickly as possible or at least to modify its character At the beginning of the epidemic, convalescent measles serum was not available, but since the reports of the use of adult whole blood and Tunnicliff immune goat serum in measles prophylaxis were so encouraging, it was decided to employ these agents Accordingly 112 infants, ranging from 4 to 18 months and fifty-six children from 2 to 4 years of age received intramuscular injections of 30 cc of adult whole blood Tunnicliff antimeasles goat serum, which was obtained through the courtesy of Dr Ruth Tunnicliff, was inoculated into thirty-eight children, each receiving 8 cc Normal goat serum was used in eleven children as a control As the epidemic progressed we were able to obtain convalescent serum from some of the children and also from three of the nurses who developed the disease This form of treatment was given to sixty-four children Twenty-three children did not receive injections of any kind Thus an opportunity presented itself to compare the relative value of various prophylactic agents

ADULT WHOLE BLOOD

Blood was usually taken from the parent of the child who was to be inoculated, after a careful history had been obtained to eliminate the possibility of tuberculosis or syphilis Thirty cubic centimeters of blood was withdrawn from the arm under aseptic precautions and collected into a flask which contained a few crystals of sodium citrate The blood was either used immediately or kept in a refrigerator and used within twenty-four hours Fifteen cubic centimeters was injected into the upper and inner quadrant of each buttock, as a larger amount is apt to cause discomfort and even necrosis It may be added that the injections were well tolerated and that in no instance was a rise in temperature noted

Of the fifty-six children who received 30 cc of adult whole blood, forty-three, or 77 per cent, developed measles As table 1 indicates, twenty-three, or 53 per cent, of these cases were of the modified or attenuated type Thirteen children remained free from the disease, although they had been exposed to measles throughout the epidemic, which lasted two months Since the entire uninoculated group of twenty-three children came down with measles which in no instance could be classed as attenuated (table 2) it must be concluded that thirty-six, or 64 per cent, of this group were definitely benefited by the use of adult whole blood It should be stated that the attenuation resulting from this blood was not quite so pronounced as that noted from the use of convalescent serum The increase in temperature in the attenuated disease was moderate, with an average duration of three days, the catarrhal symptoms were either absent or very mild, Koplik spots were present in about 50 per cent of the cases, the rash in some instances was scanty, in others widespread but never confluent Of great importance was the fact that these children did not appear ill They were almost invariably either sitting or standing in their beds and showed no signs of discomfort No complications developed

It may be noted from table 1 that attenuation depends on the day of the incubation period on which the injection is given, when it was given in the course of the first five days or from one to eight days prior to incuba-

Table 1—*Clinical Data and Course of Forty-Three Cases of Measles Among Children Who Received Adult Blood*

		Day of Inoculation in Relation to Incubation Period						
Name	Ward	Before	During	Koplik Spots	Eruption	Fever Days	Course	Comment
C T	2		10	+	++±	10	Moderate	
G N	6		9	—	+++	5	Moderate	
B R	6		8	+	++±	3	Moderate	
S W	6		7	+	+±	3	Mild	
H L	6		7	+	+++	3	Mild	
S T	6		7	+	+±	3	Mild	
P Q	2		7	+	+++	3	Moderate	
M K.	6		5	+	+	4	Attenuated	
T R	6		5	+	+	2	Attenuated	
P P	6		5	+	+	3	Attenuated	
L R	6		5	—	+	1	Attenuated	
E. H	6		4	+	++	5	Attenuated	
R F	6		4	—	++	5	Attenuated	
H R	6		2	+	+	4	Attenuated	
C C	6		1	+	+	3	Attenuated	
M A	6	1		+	++	5	Moderate	20 cc blood
R K	2	1		—	+±	7	Attenuated	
R. L	2	2		—	++	6	Mild	
B S	Inf *	3		—	+±	2	Attenuated	
A I	2	4		—	+±	4	Attenuated	
H D	Inf	4		—	+	2	Attenuated	
H S	Inf	4		—	++	4	Attenuated	
W R	2	4		+	++	3	Attenuated	
S A	2	4		+	++	2	Attenuated	
A G	2	4		+	++	3	Attenuated	
M B	2	4		+	++	3	Attenuated	
W L	2	4		+	++	4	Attenuated	
M S	Inf	6		—	+±	4	Attenuated	
N D	Inf	6		—	+	4	Attenuated	
H R	2	6		+	++	9	Moderate	Otitis media
E B	9	6		—	++±	4	Attenuated	
R G	2	6		—	++	5	Attenuated	
P T	6	8		—	+	1	Attenuated	
E A.	9	12		+	++±	9	Moderate	Otitis media
M S	Inf	15		+	++	9	Moderate	
M J	Inf	16		+	++±	8	Moderate	
J T	Inf	16		+	++	9	Moderate	
D R	Inf	19		+	++	9	Moderate	Otitis media
H E	Inf	19		+	++	10	Moderate	Otitis media
S M	Inf	19		+	++	10	Moderate	Otitis media
A. L	Inf	21		+	++±	6	Moderate	
Y G	Inf	21		+	++	6	Moderate	Hemorrhagic rash
F M	7	23		+	+++	7	Severe	Otitis media adenitis

* Infirmary

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17 Tunnicliff Ruth and Hoyne A. L. Prevention of Measles by Immune Goat Serum J A M A. 87 2139 (Dec 25) 1926

18 Peterman M G Prevention of Measles Am J Dis Child 36: 123 1928

19 Halpern L J The Prevention and Modification of Measles by Measles Antidiplococcus Goat Serum J A M A 90 1109 1928

20 Hoyne, A. L. and Peacock Silber Prevention and Modification of Measles with Antimeasles Diplococcus Goat Serum Am J Dis Child. 35 1021 (June) 1928

21 Peterman M G Antimeasles Diplococcus Goat Serum (Tunnicliff) Am J Dis Child. 39 294 (Feb.) 1930

tion, modification resulted in twenty-three out of twenty-six children Of the three children who failed to develop "attenuated measles," one received only 20 cc of blood In almost all of the papers dealing with prophylaxis in measles, the day of the incubation period has been determined by computing the number of days that the child had been exposed This method may hold good for children exposed to measles in private homes but cannot be utilized in institutions or hospitals where children are harbored in large wards and therefore are not so apt to come into intimate contact with the patient having measles Some may contract the disease on the first day of exposure, others as late as the seventh, and still others may not develop it in spite of the fact that they have remained in the same ward during the entire course of the disease, only to come down with measles at a subsequent outbreak It is possible that these children had a partial immunity at the beginning of the epidemic and required intensive or repeated exposures before developing the disease This feature is well illustrated in the study of the control group in which some developed measles only after a second outbreak in the ward It is obvious, then, that the number of days of exposure cannot serve as a guide for determining the day of the incubation period of measles We were able to determine with a fair degree of accuracy the day of the incubation period on which the injection of blood was given only in those children who came down with measles The method employed was as follows By subtracting fifteen days from the time of appearance of the rash, the first day of incubation was obtained It should be added that we were able to trace a number of cases of attenuated measles to their original source and that it was found that the incubation period in these cases was not prolonged Degkwitz [2] also found that the incubation period was normal in attenuated measles which resulted from injections of adult blood In our opinion the unusually long incubation period observed by some authors in this type of measles is not correct, the disease presumably having resulted from a later contact

Table 2—*Clinical Data and Course of Twenty-Three Cases of Measles Among Children Not Receiving Prophylactic Inoculations*

Name	Ward	Koplik Spots	Fever Days	Eruption	Course	Comment
F L	2	+	4	++	Mild	
M M	2	+	5	++	Marked	Enteritis and otitis media
H B	6	+	5	+++	Marked	Otitis media
R M	6	+	10	++	Marked	
D K	6	+	2	+++	Mild	
K S	6	+	5	+++	Moderate	
P B	9	+	8	+++	Marked	
Y G	9	+	9	+++	Marked	Child was toxic otitis media
E B	Inf	+	14	++±	Marked	Otitis media
E F	Inf	+	6	++	Moderate	
B H	Inf	+	9	+++	Marked	Otitis media
F H	Inf	+	7	++	Moderate	
B Y	Inf	+	5	++	Mild	
M K	11	+	[illegible]	++++	Marked	
D S	11	+	3	++	Moderate	
F K	9	+	7	++±	Marked	
S F	Inf	+	14	++±	Marked	Otitis media
L M	10	+	4	++	Moderate	
H W	10	+	8	++±	Marked	
M M	10	+	10	+	Marked	Bronchopneumonia died
H H	Inf	+	8	++±	Marked	
P M	Inf	+	6	++	Marked	
H W	Inf	+	17	++	Marked	Bronchopneumonia

A glance at table 1 shows that if infection takes place later than eight days after the inoculations of blood, no beneficial effect results This point must be borne in mind, especially in institutions and hospitals where there are usually a number of successive outbreaks, and in order to insure attenuation of measles in almost every child who develops the disease, a practical method would be to repeat the injections of blood every twelve days in those who have not yet come down with the disease It is obvious that this procedure would have to be carried out at the expense of reinoculating some children who either have already developed complete protection or are about to come down with attenuated measles In private homes, however, since children are in closer contact, infection almost always follows exposure to measles, and therefore it will rarely be necessary to repeat the administration of blood

Nineteen children, or 34 per cent of those who received adult whole blood, were not protected Seven of these received the injection of blood too late, in other words from the seventh to the tenth day of the incubation period, whereas ten were infected with measles from twelve to twenty-three days after receiving the inoculation and thus were deprived of the protective value of the blood

Of this group, thirteen children, or 23 per cent who did not develop measles, had been in the institution since birth, so that we are certain that they had never had measles They were in various wards and were repeatedly exposed to the disease Since, as stated, the entire control group developed measles, protection must be ascribed to the injection of blood It is conceivable that these children had a partial immunity at the outset and that with the injection of blood they received sufficient antibodies to carry them over the epidemic The possibility that the blood which these children received contained a particularly high titer of measles immune bodies must also be considered How long these children would have remained protected had the epidemic persisted for a longer period is mere conjecture In this connection, it is interesting that two children suffering from pneumonia who were given transfusions of blood in amounts of 400 cc also remained protected throughout the epidemic, although actively exposed

The proportion of complications in this group was 14 per cent, as compared to 35 in the control group It may be noted that the complications occurred only in those children who did not come down with the attenuated form of measles The complications consisted mainly of otitis media, whereas in the control group two children also developed bronchopneumonia Had we known that the protection with 30 cc of adult whole blood does not last longer than eight days, we could have diminished the number of complications by repeating the injections

The importance of the use of a prophylactic agent in infants has been emphasized Since it was desirable to confer as high a degree of protection as possible on the infants, the same amount of blood was used as in the older children One hundred and twelve infants, ranging from 4 to 18 months of age, who were housed in five wards, were given injections of 30 cc of adult whole blood The seriousness of measles in infants did not warrant the formation of a control group Not one of these infants came down with measles It must be added, however, that there was no active exposure to measles in these wards, so that it cannot be concluded that these infants were protected solely by the blood injections In the past epidemics the infant wards were invariably involved, so we believe that the use of adult whole blood was in a large measure responsible for the freedom from measles It may be mentioned that Gerlach and Kovacs reported complete protection in 90 per cent of actively exposed infants who were given injections of from 20 to 30 cc of adult whole blood

CONVALESCENT MEASLES SERUM

Sixty children received 6 cc of convalescent measles serum, which was obtained either ten days or thirty days after defervescence Forty-four, or 73 per cent remained completely protected Of the sixteen children who developed the disease, fourteen came down with a markedly attenuated form of measles One of the two children who developed moderate measles received convalescent serum on the last day of the incubation period No complications were observed in this group It may be added that the thirty day serum seemed to be just as potent as the ten day serum

TABLE 3—*Clinical Data and Course of Measles Among Children Who Received Immune Goat Serum (Tunnicliff)*

Name	Ward	Day of Inoculation in Relation to Incubation Period: Before	During	Koplik Spots	Eruption	Fever Days	Course	Comment
I S	Inf		1	+	+++	8	Marked	
Y G	Inf		1	+	++	7	Moderate	
I P	Inf		1	+	+++	8	Moderate	
R. L	Inf		1	+	++	7	Moderate	Otitis media
N F	Inf		1	+	++	7	Moderate	
J S	9		1	+	++	8	Marked	Otitis media toxic
B H	9		1	+	++	5	Moderate	
F L	9		1	+	++±	5	Marked	Toxic
S R	9		1	+	++	5	Marked	Toxic serum sickness
R R	9		1	+	++++	10	Marked	Otitis media anuria serum sickness
L L	2		1	+	++	5	Marked	Otitis media
F K	9		2	+	+++	12	Marked	Bronchopneumonia toxic serum sickness
F F	Inf		2	+	+++	5	Moderate	
P W	Inf		2	+	+++	7	Moderate	
F P	Inf		2	+	+++	8	Marked	
D K	Inf		3	+	++	6	Moderate	
H N	9		3	±	++	7	Moderate	
L S	9		3	+	++	8	Marked	Otitis media toxic
B T	Inf		3	+	+++	7	Marked	Toxic marked serum sickness
B O	Inf		3	+	++++	6	Marked	Toxic marked serum sickness
G E	Inf	1		+	+++	12	Marked	Otitis media toxic, serum sickness
A O	Inf	1		+	++	7	Moderate	
S G	Inf	1		+	++	7	Moderate	
S H	9	1		+	++++	5	Marked	
A S	2	1		+	+++	10	Marked	Otitis media
R F	2	1		+	++	7	Marked	Otitis media
H A	Inf	1		+	++	5	Moderate	
R P	9	2		+	++±	7	Marked	Toxic
S B	Inf	3		+	+++	5	Moderate	
O F	11	4		+	++	5	Moderate	
L S	Inf	4		+	++	8	Moderate	Otitis media
S E	9	6		+	++	5	Moderate	
R S	9	8		+	++++	9	Marked	
I B	11	13		+	++	7	Moderate	Otitis media
D B	11	14		+	++	4	Moderate	
R S	11	14		−	++	6	Moderate	
R G	11	15		+	++±	5	Moderate	
B W	11	18		+	+++	6	Moderate	

TUNNICLIFF SERUM

Thirty-eight children were given 8 cc of immune goat serum (Tunnicliff) As indicated in table 3 the entire group developed measles, seventeen of the severe and the others of the moderate type Twenty were given the serum during the first three days of the incubation period, while twelve were inoculated from one to six days and six from eight to eighteen days prior to infection Several of these children were extremely sick and the group as a whole presented the most serious cases of measles in the institution The temperature ranged from 102 to 104 F with an average duration of seven days Serum sickness was observed in six cases and was marked Ten children developed otitis media and one bronchopneumonia, the proportion of complications being 29 per cent These children were housed in the same wards in which adult whole blood and convalescent measles serum were employed and thus a fair opportunity seems to be afforded of comparing the relative value of these prophylactic agents (table 4) The good results with the use of convalescent serum and adult whole blood stand out in striking comparison to the results with Tunnicliff serum These results differ widely from those reported by the authors previously mentioned, and we are at a loss how to explain the divergence It may be added that, in a discussion of a paper on measles prophylaxis,[22] Park stated that he had not obtained favorable results with this serum, although he did not present data

TABLE 4—*Comparison of the Results of Various Prophylactic Agents Against Measles According to Individual Wards*

Ward	No of Children Inoculated	Type of Inoculation	No of Children With Measles	Number With Attenuated Measles	Number Completely Protected	Number With Complications
11	26	20 convalescent serum	8	6	12	0
		6 Tunnicliff serum	6	0	0	1
7	17	16 convalescent serum	3	2	13	2
		1 adult blood	1	0	0	1
6	22	22 adult blood	15	9	7	0
2	25	16 adult blood	12	8	4	2
		4 Tunnicliff serum	4	0	0	3
		5 normal goat serum	4	0	1	2
9	23	2 adult blood	2	1	0	1
		6 normal goat serum	6	0	0	2
		15 Tunnicliff serum	15	0	0	4
10	16	16 convalescent serum	2	2	14	0
Inf	38	8 convalescent serum	3	3	5	0
		13 Tunnicliff serum	13	0	0	2
		2 normal goat serum	2	0	0	0
		15 adult blood	13	4	2	4

TABLE 5—*Incidence and Course of Measles Among Treated and Nontreated Children*

Type of Treatment	Number of Children Injected	Number with Measles	Per Cent with Measles	Course: Attenuated	Mild	Moderate	Severe	Per Cent Attenuated	Number with Complications	Per Cent with Complications
Convalescent serum 6 cc	60	16	27	14	0	2	0	88	0	0
Whole blood 30 cc	56	43	[illegible]	23	4	15	1	53	6	11
Tunnicliff serum 8 cc	38	38	100	0	0	21	17	0	11	29
Normal goat serum 8 cc	13	12	92	0	0	5	7	0	4	[illegible]
None	23	23	100	0	3	5	15	0	8	[illegible]

Of the thirteen children who were given 8 cc of normal goat serum twelve developed measles, seven were marked and the remainder were moderate cases One child escaped infection, although as far as we know it had never had measles Serum sickness was noted in three and otitis media in four instances

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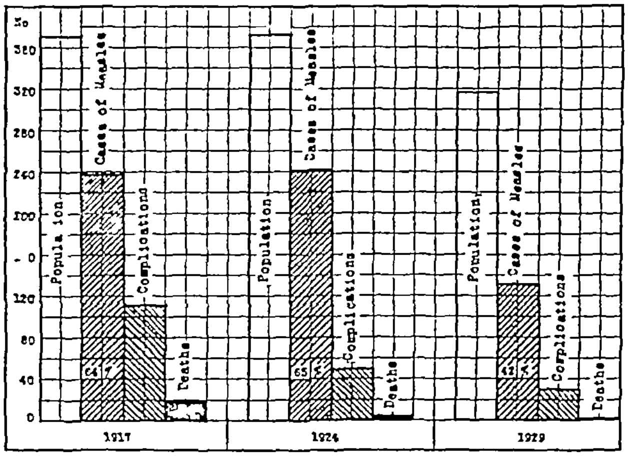
[22] Silverman A C Serum Prophylaxis in a Measles Epidemic J A M A 91 1786 (Dec 8) 1928

The comparative value of convalescent serum, adult whole blood and immune goat serum (Tunnicliff) is clearly brought out in table 5 Since the entire group of thirty-eight children who received immune goat serum and twelve of thirteen who received normal goat serum were to no extent protected, the control group may be considered as consisting of seventy-four children, among whom seventy-three, or 99 per cent, developed typical measles This high incidence in the control group permits one to draw definite conclusions as to the efficacy of convalescent measles serum and adult whole blood in this epidemic Convalescent measles serum was of particular value in preventing the disease, whereas adult blood was effective in bringing about attenuated measles in a high percentage of the children This form of the disease is highly desirable for children of private homes, since permanent immunity also results from attenuated measles In institutions and hospitals, complete protection should be the goal With the injection of 30 cc of blood, complete prevention was brought about in only 23 per cent of the children Had we used a larger amount the percentage of complete protection undoubtedly would have been higher Since it is not practical to inject intramuscularly more than 30 cc of whole blood it is necessary to use serum if a larger amount of antibodies is desired According to Karelitz and Levin[8] inoculations of from 30 to 40 cc of serum during the first four days and of from 40 to 50 cc during the fifth to the seventh days of the incubation period bring about complete protection in children aged 3 years or over



A comparison of the end results of three epidemics of measles which occurred in the institution during the years *1917 1924* and *1929*

It may be of interest to compare the results of this epidemic with those of two previous outbreaks, one occurring in 1917 and the other in 1924, as presented in the accompanying chart In 1917 no prophylactic treatment was employed Of 372 exposed children, 238 came down with measles, an incidence of 64 per cent Complications occurred in 118 children, or 47 per cent of the cases, and consisted chiefly of pneumonia and otitis media There were nineteen deaths, a mortality of 8 per cent During the 1924 epidemic, convalescent whole blood was employed and the results were published in detail by Haas and Blum[23] The incidence in this epidemic was not diminished A large number of the children, however, developed attenuated measles and as a result there was a considerable reduction in the morbidity and mortality In the present epidemic, prophylaxis was employed on a greater scale and the incidence of measles was reduced to 42 per cent The complications were less numerous and milder than in the 1924 epidemic Only one death occurred during the entire epidemic The complications occurred chiefly among the untreated children

SUMMARY

An epidemic of measles broke out in an institution harboring approximately 325 children, 150 under 2 years and the others from 2 to 4 years of age, the epidemic lasted for a period of two months, and of 318 susceptible children 132, or 42 per cent, developed the disease

Of fifty-six children actively exposed who received 30 cc of adult whole blood, forty-three developed measles Since twenty-three of the fifty-six children developed an attenuated form of measles and thirteen were fully protected, we conclude that thirty-six children, or 64 per cent of this group, were benefited by these injections When the blood was injected in the course of the first five days of the incubation period or from one to eight days prior to incubation, attenuation of measles resulted in twenty-three of the twenty-six children However, when the injection of blood was not given within the times specified, attenuation did not result The modification of measles due to adult blood was not quite so pronounced as that following the use of convalescent measles serum The percentage of complications in this group was eleven, as compared to thirty-five in the control group, and these complications occurred only in those children who did not develop attenuated measles One hundred and twelve infants who were not actively exposed received 30 cc of adult blood and remained free from measles

The entire group of thirty-eight children who received 8 cc of immune goat serum (Tunnicliff) developed typical measles in spite of the fact that twenty were given the serum within the first three days of the incubation period The percentage of complications in those receiving this serum was approximately as high as that in the control group Of thirteen children who received normal goat serum, twelve came down with typical measles

Sixty children received 6 cc of convalescent measles serum and of these forty-four, or 73 per cent, remained completely protected, and fourteen, or 23 per cent, developed markedly attenuated measles, thus 96 per cent of the children of this group were protected by the use of convalescent measles serum No complications were observed among these children

Among twenty-three children who received no blood or serum, all developed typical measles Complications were noted in 35 per cent of these children, two developing bronchopneumonia

CONCLUSIONS

1 Convalescent measles serum is the most effective prophylactic measure against measles, but its application is limited because of its lack of availability

2 The blood of normal adults who have previously had measles is of great value in bringing about an attenuated form of measles and is the most practical method of prophylaxis

3 We failed to confer protection or to mitigate the disease by means of immune goat serum (Tunnicliff)

1749 Grand Concourse—495 West End Avenue

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[23] Haas S V and Blum Julius The Prophylactic Value of Blood of Convalescents in Measles *J A M A* 87 558 (Aug 21) 1926

SCURVY IN ADULTS

REPORT OF TWO CASES

MANUEL G GICHNER, M D
AND
MILTON SHERRY, M D
BALTIMORE

Scurvy in adults living the usual life of urban centers is a rare disease Umber[1] in 1922 remarked that during the fifty-eight years of the existence of the Berlin Medical Society, no report of scurvy in adults had ever been presented before that body, except one that described an instance in an exploring expedition at the antipodes In the cities of the Atlantic seaboard the disease appears somewhat more frequently, twenty-two cases of scurvy in individuals over 20 years of age were diagnosed at the Boston City Hospital and at the Massachusetts General Hospital between the years 1923 and 1928 This low incidence of the disease is not surprising The average dietary supplies an ample supply of antiscorbutic vitamin and it has been repeatedly shown that a deficiency in the ingestion of this vitamin must continue for from four to seven months before the first definite symptoms of the malady develop Thus, scurvy will develop only in those who, for one reason or another, do not take the same diet as do others living in the same environment

The reasons for such dietetic errors have been variously described Economic factors are stressed by Shattuck[2] and by Hess[3] It is not, however, among the destitute, tramps and vagrants that these cases are seen Frequently "dietetic eccentricity" forms part of the abnormal behavior of maladjusted personalities and the high incidence of scurvy in institutions for the insane (commented on by Hess) may not, we believe, be attributable always to inefficient management In one group of cases, a typical history is obtained of a rather "shut-in" person of solitary habits who prepares his own meals and eats simple food of high caloric value Meulengracht[4] has reported a series of cases of scurvy in "men living alone," and Shattuck noted eight widows and widowers among the thirty-one scorbutic patients who comprise his series Another group of cases may be expected to occur among those with "gastric neuroses," individuals who limit their diet in fantastic attempts at self-treatment It is improbable that cases of avitaminosis develop often as a result of dietary restriction prescribed by physicians

Our first case illustrates dietetic errors in a Russian immigrant widower in the sixth decade of life, who led a solitary existence and prepared his own meals, our second patient was a neurotic woman, aged 23, who complained of ill defined gastric symptoms

REPORT OF CASES

Case 1—J R., a Russian Jewish widower, aged 56, a tailor, was admitted to the Sinai Hospital May 11 1928, because of pains in the muscles of the legs especially behind the knee joints These pains were aggravated by walking The family history was essentially negative The patient had had transient hoarseness at intervals since 1916 and had suffered from chronic constipation for twenty years The left eye had been sightless for eight years There had been occasional bleeding from the right side of the nose His usual weight was 185 pounds (84 Kg) his weight on admission was 140 pounds (63.5 Kg) Since 1925 there had been increasing painless weakness of the legs, and by January, 1928 the weakness had increased until he was unable to walk five blocks At the beginning of March 1928 the pain was so intense that he was forced to remain in bed, with rest the pain disappeared but when physical activity was resumed the pain promptly reappeared and he had been confined to bed for three weeks prior to his admission to the hospital

At the time of his admission the temperature was 99 F the pulse 88 a minute the respiration 22 a minute and the blood pressure 155 systolic and 90 diastolic There was marked pallor of the skin and there was an acneform eruption over the body The gums were spongy and hypertrophied There was marked dental caries many teeth were missing and fetor oris was marked There was a small ulceration in the left nostril Modification of the percussion note and of the breath sounds over the apex of the right lung were present as evidence of an old fibrosis of the apex There were extensive ecchymoses about both popliteal fossae and these areas as well as the calves of the legs were extremely painful on pressure The right knee jerk could not be elicited

Examination of the blood at the time of admission showed hemoglobin, 60 per cent red blood cells 2 528 000 white blood cells 10 000 with a differential count of 66 per cent polymorphonuclears 7 per cent large lymphocytes 23 per cent small lymphocytes and 4 per cent large mononuclears and transitionals and a platelet count of 280 000 per cubic millimeter The clotting time was one and one-half minutes (Howell) the bleeding time one minute. There was no abnormal fragility of the red cells The urine was normal The phenolsulphonphthalein output was 50 per cent in two hours The blood urea nitrogen was 19 60 mg per hundred cubic centimeters Roentgen studies of the chest showed fibroid infiltration of the right apex A roentgenogram of the left leg did not show any pathologic changes The dentist reported hemorrhagic hypertrophic gingivitis due to a chronic periodontitis or to a suppurative pyorrhea alveolaris' Roentgenographic examination of the teeth showed resorption of the alveolar process extending to and involving the apical third of all the roots

Table 1—*Blood Changes in Case 1*

	5/14/28	5/20/28	
Hemoglobin	58%	68%	80%
Red blood cells	3 100 000	2 840 000	3 712 000
White blood cells	11 000	8 000	7 000
Differential formula			
Polymorphonuclears	78%	69%	78%
Large lymphocytes	4%	10%	2%
Small lymphocytes	11%	17%	16%
Large mononuclears	7%	4%	4%
Transitionals	7%		

May 14, the house officer noted that the patient talked incoherently and seemed disoriented A tentative diagnosis of scurvy was made and the patient was given one glass of orange juice with each meal By May 28, two weeks after this treatment was begun the patient showed a remarkable improvement The sponginess of the gums and the fetor oris had disappeared the ecchymoses, although still present, were smaller and the legs were no longer painful on pressure The patient was still unable to walk, because of general weakness By June 8 the mouth was completely normal and the patient was able to stand unassisted It was not until June 16 that it was ascertained that the patient, though living with relatives was accustomed to take his meals in his own room and that he had not eaten any fresh fruits or vegetables in the past five years

The secondary anemia disappeared as evidenced by the blood counts in table 1 This improvement may have been due in part to a course of twelve doses of sodium cacodylate, ¼ grain (16 mg) each, begun May 18

The patient was discharged cured June 23

Case 2—Miss J R., American aged 23 a labeler in a canning factory, was admitted to the West Baltimore General Hospital Aug 20 1928 because of stiffness of the right knee and of pain and swelling in both knee and ankle joints and of continuous vaginal bleeding for three months The family history was essentially negative She stated that she had been perfectly well until 1925 At that time she began to feel depressed and melancholy and went to her family physician, who treated her About ten months before she began to complain of a nervous stomach" and was given a special diet. She complained of fulness and of gaseous eructations and stated that "she felt full of gas all the time" She had never had nausea or spontaneous vomiting but sometimes was relieved of distention by inducing vomiting About three months before, the patient had noticed soreness and bleeding of the gums and was treated for this by a dentist Since then bluish areas had appeared on both lower extremities and particularly on the right knee She had not been able to extend the knee completely for two weeks In May, 1928, she menstruated at the regular time but the vaginal bleeding continued until the time of her admission to the hospital Insomnia, weakness, dyspnea and edema of the ankles developed, but there was no palpitation or precordial pain

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[1] Umber F Med Klin **18** 851 (July 2) 1922

[2] Shattuck G C Scurvy with Reference Especially to Adults J A M A. **90** 1861 1864 (June 9) 1928

[3] Hess A. F Scurvy Past and Present Philadelphia J B Lippincott Company 1920

[4] Meulengracht Acta med Scandinav **67** 43 (Oct. 8) 1927

When the patient was admitted to the hospital her temperature was 101 6, the pulse 94 a minute, the respiration 22 a minute and the blood pressure 104 systolic and 50 diastolic The patient was a blond, tall, well developed and well nourished There was a waxy pallor of the skin of the palpebral conjunctiva and of the lips The pallor of the buccal and of the pharyngeal mucous membranes was in striking contrast to the extreme redness of the gums The latter were spongy and bled when touched lightly The teeth were loose The abdomen was flaccid, otherwise the trunk showed no abnormalities There were numerous ecchymoses visible on the legs particularly about the ankles and in the right popliteal space The patient was unable fully to extend the right leg, although she could flex it normally Both ankles were edematous and both legs were tender on deep pressure The tendon reflexes were hyperactive No pelvic disease was apparent

Examination of the blood August 30 showed hemoglobin, 47 per cent red blood cells 2 790 000 white blood cells, 11,350, with a differential count of 79 per cent polymorphonuclears, 2 per cent polymorphonuclear eosinophils, 2 per cent polymorphonuclear basophils 12 per cent small lymphocytes, and 3 per cent transitionals The clotting time varied between four and six minutes (Howell) The clot retracted normally The urine on admission showed a trace of albumin The phenolsulphonphthalein output was 40 per cent in two hours The blood urea nitrogen was 29 1 mg per hundred cubic centimeters Gastric analysis showed 6 per cent free hydrochloric acid a total acidity of 18 per cent and a combined acidity of 12 per cent The capillary resistance test was positive, marked petechial spots appearing in the cubital fossa after constriction of the upper arm at 80 mm of mercury for three minutes

Table 2—*Blood Changes in Case 2*

	9/1	9/7	9/11	9/15	9/20	9/24	10/2
Hemoglobin		47%	56%	69%	69%	69%	70%
Red blood cells		2 880 000	3 130 000	3 390 000	3 630 000	3 500 000	3 400 000
White blood cells		8 700	9 300			13 050	
Differential formula							
Polymorphonuclears	72%	74%				67%	
Polymorphonuclear eosinophils							
Polymorphonuclear basophils	2%						
Small lymphocytes	15%	20%				19%	
Large lymphocytes	3%	3%				11%	
Large mononuclears	2%						
Transitionals	6%	3%				1%	

Further investigation elicited the fact that the patient had for the past few years lived almost exclusively on a diet of crackers and milk A diagnosis of scurvy was made and the patient was given a general diet with fresh orange juice, in addition sodium cacodylate and solution of potassium arsenite were administered

Improvement was rapid and striking the secondary anemia disappeared, the subsequent blood counts being as given in table 2

The vaginal bleeding ceased on the sixth day after the initiation of treatment and the pain in the extremities ceased on the tenth day On the sixteenth day, the mouth was normal By the twentieth day the capillary resistance test was negative The ecchymoses had completely disappeared by the twenty-sixth day when the patient was discharged cured

COMMENT

The relative rarity of scurvy in adults and the greater frequency of other diseases characterized by hemorrhage leads often to a tentative diagnosis of purpura hemorrhagica, symptomatic purpura, hemophilia, anemia, leukemia or sepsis before scurvy is considered It should be emphasized that an exact and careful inquiry into the nutritional habits of patients is an important part of the collation of a history In the two cases reported, the essential illuminating fact that there had been for a long time a dietary insufficiency was brought out only after careful studies had excluded as causal the more usual syndromes in which the presenting symptoms occur

Sinai Hospital

THE DIAGNOSTIC VALUE OF THE COMPLEMENT FIXATION TEST IN AMEBIC INFECTIONS *

CHARLES F CRAIG, M D
Colonel Medical Corps U S Army
WASHINGTON, D C

In July, 1927, I[1] called attention to the fact that alcoholic extracts of cultures of *Endameba histolytica,* the cause of amebic dysentery, possessed marked complement-binding power when used as an antigen in complement fixation tests of individuals infected with this parasite In January, 1928,[2] and again in July, 1928,[3] I published papers giving the results of this complement fixation test, and, in September, 1929,[4] a paper giving the technic and the results of the test up to July, 1929

It is my purpose in this paper to give the results obtained with this complement fixation test to March 30, 1930, together with a discussion of its value in the diagnosis of infections with *Endameba histolytica,* based on my experience with it over a period of nearly three years

TECHNIC

The exact technic of the test has been described in one of the publications[4] referred to, but it may be stated that the general technic is the same as that employed in the standard method for performing the complement fixation test for syphilis, used in all of the U S Army laboratories and described in my book on the Wassermann test[5] The human hemolytic system is used The blood serums to be tested are inactivated by being heated in a water bath at 56 C for one-half hour, and the antigenic extract is used without dilution because of its weakness in antigenic property.

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* From the Department of Preventive Medicine and Clinical Pathology Army Medical School Army Medical Center

[1] Craig C F Am. J Trop Med 7: 225 (July) 1927

[2] Craig C F Am J Trop Med 8 29 (Jan) 1928

[3] Craig C F Proc. Nat Acad Sc **14** 520 (July) 1928

[4] Craig C F Am J Trop Med 9 277 (Sept.) 1929

[5] Craig C F The Wassermann Test ed. 2 St. Louis C V Mosby Company 1921

MATERIAL

The individuals tested have been mostly patients in the Walter Reed U. S. Army General Hospital, where the test is being used as a semiroutine test in suspicious cases. The patients tested have been suffering from a great variety of disease conditions, and in addition numerous normal persons have been used as controls. During the experimental work on the reaction, the serums were taken at random from specimens submitted to the serologic laboratory of the Army Medical School by the hospital for the Wassermann and Kahn tests, but during the past year and a half, as the results appeared to be valuable in diagnosis, most of the serums tested have been from patients referred to our laboratory for that purpose. After each serum has been tested, a specimen of the feces of the patient, whether the result of the test was positive or negative, has been examined microscopically and culturally for *Endameba histolytica*. Thus, all of the results reported in this communication have been checked by such examinations of the feces of the individuals furnishing the blood serums tested.

RESULTS OF THE TEST

More than a thousand serums from as many individuals have been tested, but this report concerns only those tests in which the feces have been checked for the parasite, numbering 689, of which eighty-four, or approximately 12 per cent, gave a positive reaction, and 605, or 88 per cent, gave a negative reaction.

The character of the reaction with this test is usually very clear cut, being either 3 plus or 4 plus when read on a 4 plus scale. Thus, of the eighty-four positive cases, no less than seventy-one gave a 4 plus reaction and the remainder a 3 plus reaction. It should be remembered, in considering the number of positive results, that many of the patients tested have served in tropical regions or have presented symptoms of derangement of the gastro-intestinal tract.

In the eighty-four positive cases, a check of the feces for *Endameba histolytica* resulted in the demonstration of this parasite in seventy-seven cases, or almost 92 per cent. In thirteen, or about 8 per cent, we were unable to find the parasite, but this negative finding cannot be considered absolutely conclusive because of the fact that in most of these cases it was not possible to make more than one or two examinations of the feces.

Of the eighty-four positive cases, fifty-seven showed infection with *Endameba histolytica* alone, ten were mixed infections with *Endameba histolytica* and *Endameba coli*, five with *Endameba histolytica* and *Endameba* (*Endolimax*) *nana*, two with *Endameba histolytica*, *Endameba nana* and *Endameba coli*, two with *Endameba histolytica* and *Chilomastix mesnili*, two with *Endameba histolytica* and *Giardia intestinalis*, and two with *Endameba histolytica* and *Trichomonas hominis*.

There were 605 cases in which the feces were checked that gave a negative result. In these, *Endameba histolytica* was found in five cases, or 0.8 per cent. One of these cases was a severe acute case of amebic dysentery, one was an abscess of the liver, one was symptomless, while the other two showed gastro-intestinal symptoms that were suspicious. Therefore it is evident that persons infected with this parasite do not all give a positive reaction, but the percentage is apparently very small.

Of the 605 patients giving a negative reaction there were no less than 211 or 34.8 per cent infected with other species of protozoa. Thus, there were ninety-six or 18.8 per cent, infested with *Endameba coli*; sixty or 9.9 per cent infested with *Endameba nana*; three or 0.4 per cent, infested with *Iodameba williamsi*; twenty-five or 4.1 per cent with *Chilomastix mesnili*, sixteen or 2.6 per cent, with *Trichomonas hominis* and eleven or 1.8 per cent, with *Giardia intestinalis*. There were eleven mixed infestations with *Endameba coli* and *Endameba nana*, six with *Endameba coli* and *Chilomastix mesnili*, four with *Endameba coli* and *Giardia intestinalis*, and three with *Endameba coli* and *Trichomonas hominis*.

That infestation with other species of amebas found in the intestinal tract of man does not lead to a positive complement fixation reaction with this test is evidenced by the fact that 159 of the patients giving a negative reaction, or 26.2 per cent were infested with some species of ameba other than *Endameba histolytica*.

Practically all of the 605 individuals giving a negative reaction were patients in a general hospital suffering from a wide range of acute and chronic disease conditions, so that it appears justifiable to conclude that the test is not positive in other diseases, with the exception of certain rare cases of syphilitic infection.

RELATION TO THE WASSERMANN AND KAHN REACTIONS

As the antigen used in this test is an alcoholic extract not only of *Endameba histolytica* but of the bacteria that may be growing with it in the cultures, and of material from the culture medium it was believed possible that the results obtained with the test might be due to the nonspecific substances in the extracts and similar to the results obtained in the Wassermann test with alcoholic extracts of normal tissues. For this reason, and in order to obviate such a source of error and ascertain whether the positive results were due to syphilis, a check of the serums tested has been made by subjecting them to a Wassermann and Kahn test in addition to the complement fixation test for *Endameba histolytica*. The results of this check have shown that thirteen, or 15.5 per cent of the eighty-four patients giving a positive reaction also gave a positive Wassermann and Kahn reaction, while seventy-one, or 84.5 per cent, gave a negative Wassermann and Kahn reaction. Of the 605 individuals giving a negative reaction with the complement fixation test for *Endameba histolytica*, fifty-four, or approximately 9 per cent gave a positive Wassermann and Kahn reaction, 551, or 91 per cent gave a negative Wassermann reaction, and 549, or 90.9 per cent gave a negative Kahn reaction. It will thus be seen that there were slightly more than 6 per cent positive Wassermann and Kahn reactions in those giving a positive result with the complement fixation test for *Endameba histolytica* than in those giving a negative result. It is also significant that of the thirteen individuals giving a positive reaction to all three tests, no less than eight failed to show *Endameba histolytica* in the feces although it may be stated that in these cases not more than two examinations were made of the feces. Admitting that all of these individuals were free from infection with this parasite, it would follow that the false positive results were due to infection with syphilis. However, in interpreting these figures it should be remembered that at least half of the serums tested were selected at random from specimens submitted to the serologic laboratory of the Army Medical School for the Wassermann and Kahn tests, a majority of the patients being in the venereal wards of the hospital

The considerably larger percentage of cases showing a positive reaction with this test and also a positive Wassermann and Kahn reaction, and the failure to find *Endameba histolytica* in the feces in more than half of such cases, appears to indicate that, in rare instances, patients suffering from syphilis will give a positive reaction with this test and that this disease must be eliminated in patients giving a positive reaction with this test unless the result is supported by the finding of the parasite in the feces

PRACTICAL VALUE OF THE TEST IN DIAGNOSIS

In view of the difficulty of differentiating *Endameba histolytica* from other species of ameba that commonly occur in the human intestine, it is obvious that if a serologic reaction could be elaborated which could be depended on to give a positive result in most cases of the infection, it would be of considerable value in the diagnosis of the condition Comparatively little work has been done on complement fixation in amebic infection Izar,[6] in 1914, using an aqueous antigen prepared by extracting fecal material containing *Endameba histolytica* and liver abscess pus, reported positive results with the blood serum of five infected persons and three infected cats In 1920, Hage[7] repeated Izar s experiments but was unable to confirm them and concluded that the test antigen contained too little reactive substance In 1921, Scalas[8] attempted to improve Izar s methods of preparing antigen, using an aqueous extract of mucous flakes from feces containing *Endameba histolytica* and obtained positive results in three infected persons and negative results in a case of bacillary dysentery and in a normal person These observations are the only ones that I have been able to collect from the literature on the subject, and it is evident that the antigens used could not be expected to give consistent results, owing to their weakness in antigenic substances

In our work we have endeavored to prepare an antigen which is strong enough in antigenic material to react in the majority of patients infected with this parasite, and I believe that this result has been attained, as shown by the large percentage of patients who have reacted and have been proved to be infected by the finding of the parasite in the feces While it is true that a diagnosis could have been made by the finding of the parasites in the feces, it is also true that numerous cases have been discovered by means of the complement fixation test which would otherwise have been overlooked These cases have for the most part been very important from the standpoint of diagnosis, several being instances of amebic abscess of the liver which might have been missed entirely or wrongly diagnosed, while a large number of individuals suffering from obscure intestinal conditions have been proved to be infected with *Endameba histolytica* by means of this test alone, the parasite afterward being found in the feces

When the services of a competent protozoologist or of one trained in the differentiation of the parasitic amebas of man are available, the complement fixation test would be of comparatively little practical value, but when such services are not available, it is believed that this test may be a most valuable adjunct to diagnosis It is unnecessary to stress here the difficulty of differentiating the various amebas of the human intestine, and it is most unfortunate that such differentiation is being attempted at this time by many technicians who are entirely untrained in protozoology The use of the complement fixation test, under such conditions, would be of service in checking the diagnosis made by untrained or improperly trained laboratory workers

In view of the elaboration of new and very efficient methods of treatment of amebic infection, the recognition of latent infections and infections showing atypical symptoms is of the greatest importance, as proper treatment usually results in the permanent disappearance of the parasite It is in this class of case that the complement fixation test should prove of great value when expert microscopic diagnosis cannot be obtained That the reaction is a specific one is shown not only by the positive results obtained in a large proportion of individuals infected with *Endameba histolytica* but by the fact that proper treatment, followed by the disappearance of the parasite, is also followed, within from three to six weeks, by the disappearance of the positive reaction This has been the invariable result in all of our cases that have been treated properly, and when the reaction has persisted, repeated courses of treatment have eventually resulted in the disappearance of the reaction, provided the amebas were eliminated

At the present time the practical value of the test is limited by the difficulty of preparing the antigenic extract For this purpose it is necessary to extract a large number of cultures of *Endameba histolytica,* and the cultivation of this organism is difficult even in experienced hands, especially when the cultures have to be maintained for weeks and months in order to make it possible to keep such antigenic extracts on hand It is also true that not all extracts possess enough antigenic properties to be of practical use, even though the same strain of the organism is used and the method of extraction is standardized The reason for this I am unable to state, but we have obtained several inert extracts from the same strain of *Endameba histolytica* that has given us our best antigenic extracts, although the same technic was employed in extraction Until it is possible to cultivate *Endameba histolytica* in pure culture, one must expect to obtain anomalous results at times, owing to the fact that the extracts are made from mixed cultures of the ameba and bacteria All of our extracts have been prepared from a single strain of *Endameba histolytica* first isolated by Capt J H St John nearly four years ago Whether other strains of the organism would give as good results has not been determined as yet, and it is hoped that the publication of this paper will stimulate research in this direction

The technic of this complement fixation test, while similar to that of other complement fixation tests, is rendered more difficult by reason of the fact that the antigenic extract is so weak in antigenic properties that it has to be used without dilution For this reason every step of the technic must be thoroughly controlled and the test should be performed only by a qualified serologist and the results checked, whenever possible, by an examination of the feces by one skilled in the differentiation of the various species of amebas occurring in the intestine of man At the present time I do not feel that this test is on the practical basis that a complement fixation test should be before it is relied on alone in the diagnosis of a specific infection The difficulties inherent in the preparation of the antigen and in the technic are such that in its present stage of development it could be performed only in laboratories where the services of a serologist and protozoologist are available However, it is felt that further research will simplify the technic of preparing the antigenic extract and that eventually the test will be comparable to the complement fixation test for syphilis as regards practical utility

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[6] Izar G Arch f Schiffs u Tropen Hyg **18** 36 1914

[7] Hage F Deutsche med Wchnschr **47** 682 (June 17) 1920

[8] Scalas L Riforma med **37** 103 (Jan 29) 1921

PREMENSTRUAL ELEVATION OF TEMPERATURE IN THE TUBERCULOUS WOMAN

EDWIN M JAMESON MD
SARANAC LAKE, N Y

DONALD A BRISTOL MD
AND
SUSAN A CAVENAUGH
LAKE KUSHAQUA N Y

The lack of any clear cut conception of the temperature changes to be expected during the days of and preceding the menses of normal and tuberculous women makes an analysis of a representative group of patients desirable While it is well known in a general way that the woman suffering from tuberculosis tends to have a slightly elevated temperature during the premenstrual week, there is a strange diversity of opinion regarding the degree of elevation to be expected in patients who eventually go on to recovery, the duration of the rise, its relation to the menses, and the influence, if any, of the amount of tuberculosis which the patient presents

Bezançon's[1] careful study of the temperature variations in the normal organism presented a number of fundamental facts Using the rectal temperature, he established as normal values, after at least one hour of repose, the following between 7 and 8 a m, from 97 9 to 98 2 F, between 2 and 6 p m, from 98 9 to 99 3 F A temperature of 99 5 is a little too high and 100 is definitely pathologic, around 9 p m the temperature falls again to 98 6 He regards the rectal and vaginal temperatures as usually being 0 2 degree higher than those taken by mouth He found that intellectual work raises the temperature as much as 0 1 degree C in one hour and that digestion had but little influence unless the patient was suffering from indigestion or the diet was rich in carbohydrates, proteins or sugars

Wunderlich,[2] after having indicated that normal menstruation in healthy women ordinarily has no effect on the body temperature, adds that sometimes there are rises in temperature during the menses which are sometimes accompanied by other functional disturbances and sometimes constitute the only pathologic phenomenon

Reml[2] studied the temperature curves of eight women whom he considered healthy and concluded that the temperature rose premenstrually in many cases and fell gradually during menstruation Rabuteau[2] also maintained that there was really a premenstrual rise and a menstrual lowering of temperature in even the healthiest women

The work of Giles,[2] who studied fifty periods in forty-five women, shows that the temperature reaches its minimum about the middle of the intermenstrual period rises gradually to attain its maximum two days before the menses appear, and then falls abruptly the evening before the appearance of the menses The temperature then rises slowly during the first week following the menstrual flow to fall again and reach its minimum about the middle of the intermenstrual period

Mme Francillon[2] on the contrary, found no characteristic change and Riebold after taking the temperatures of 2 000 sick women during the days that preceded the menses over a period of two years stated that thirty-seven of the eighty-seven women in his series who had premenstrual fever three days before the onset of the menses showed tuberculous lesions and that the other fifty had some pathologic condition not stated In only four cases did he find a premenstrual fever in normal healthy women, and here he raises the question of constipation

Bezançon, after reviewing the reports of all the available authorities, concludes that there may be a premenstrual fever in several types of women who are not tuberculous and that a premenstrual fever does not necessarily indicate even a latent tuberculosis He feels that in these so-called susceptible patients the premenstrual rise in temperature begins with the rupture of the graafian follicle and proceeds with the formation of the corpus luteum, whose secretion is a vasodilator And finally, as he points out the synergistic action of the thyroid must be taken into consideration, as a veritable state of hyperthyroidism latent in some and marked in others, may exist It is a sympathicotonic state which explains the ease of congestive phenomena, vasomotor instability, and tendency to hyperthermia that these individuals present

It is beyond the scope of this paper to review the many and conflicting opinions regarding the question of menstrual fever in healthy and tuberculous women or to quote the often weird and naive conclusions that some writers claim to be able to draw from these temperature reactions Nevertheless, mention must be made of Kaufmann's[3] report of seventy-eight tuberculous women, in only 14 3 per cent of whom she found a premenstrual increase in temperature, while 21 4 per cent showed a variable reaction and 41 4 per cent an actual decrease, and of Beekman's[4] studies, on the other hand, of 300 tuberculous women who showed a premenstrual rise in 76 per cent of the active cases He used 98 F as the normal temperature

We have studied the records of 386 women who have been patients at the Stony Wold Sanatorium and who have been discharged with the tuberculosis apparently arrested or improved From this number, five patients 14 years of age or under who showed no premenstrual rise in temperature and in whom there might be a question whether the menses were actually established, have been subtracted Seventeen patients discharged because the diagnosis of tuberculosis was unwarranted have also been taken out of this series This leaves a total of 363 tuberculous women whose records for the entire period of their sanatorium treatment are available for study

In reviewing the records at our disposal a number of cases were found in which a subnormal temperature was the rule except during the premenstrual period when the temperature rose to 98 6 F Such cases have not been included in this report, as we regard them as being too inconclusive for our purpose.

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[1] Bezançon F La temperature normale du corps humain Ann. de med 16: 496 (Dec) 1924

[2] Quoted by Bezançon (footnote 1)

[3] Kaufmann S Premenstrual and Intermenstrual Decrease in Temperature in Tuberculosis Ztschr f Tuberk. 53 97 192 1929

[4] Beekman E. Influence of Menstruation on Temperature Curve of Tuberculous Women Ztschr f Tuberk. 52 273 368 1928

Nor have we thought it advisable to adopt the usual 98 6 F as the normal mouth temperature, believing with Butler[5] and others that each individual has his own normal body temperature and that variations should be calculated from that figure We have therefore adopted as the normal in a given case the average temperature for the month exclusive of the premenstrual week and have calculated any deviations from that figure as being due to menstruation

The oldest patient in this series was 44 and the youngest 15 The average age was 24 6 years

The cases have been classified as minimal, moderately advanced and far advanced on the basis of the standards adopted by the National Tuberculosis Association The number in each group was as follows minimal, 77, moderately advanced, 238, far advanced, 48

The incidence of premenstrual fever in these groups and for the series as a whole is shown in table 1 It will be seen that less than half of all the cases showed a premenstrual rise and that the amount of tuberculosis from which the patient was suffering was of no importance in this analysis

Table 1—*Incidence of Premenstrual Fever*

	Number	Per Cent
Total showing premenstrual rise in temperature	154	42 4
Minimal	29	37 6
Moderately advanced	108	45 8
Far advanced	17	35 4

One patient in the nontuberculous group showed a rise in temperature from 98 to 99 8 F, which began from seven to twelve days before the menses started and fell the day the flow was established As no further data are available to explain this variation from the remainder of the nontuberculous group, we withhold any comment

The extent of the premenstrual rise in temperature, the number of days that the increase in temperature became manifest before the menses appeared and the duration of the rise is shown in table 2 Here again the extent of the tuberculous lesion seemed to have but little influence—a result quite different from that which we had anticipated

Table 2—*Variations in Premenstrual Rise in Temperature*

	Premenstrual Rise in Degrees F	Number of Days Before Menses That Rise Began	Duration of Rise in Days
Minimal	1 41	9 36	8 81
Moderately advanced	1 29	8 56	7 68
Far advanced	1 60	8 85	7 38

We have been unable to classify our cases into the clear cut groups described by Caussimon,[6] nor do we believe that the presence or absence of a premenstrual fever is of much prognostic significance

SUMMARY AND CONCLUSIONS

The records of 363 tuberculous women have been reviewed with especial reference to the occurrence of a premenstrual fever The cases were subdivided according to the classification of the National Tuberculosis Association, and the incidence of a premenstrual rise in temperature, the duration of such a rise and the number of days before the onset of the menses that the rise occurred were determined

From the results of this analysis of the sanatorium records of 363 tuberculous women who were discharged with the disease apparently arrested or improved, we conclude that

1 Some premenstrual rise in temperature is shown by 42 4 per cent of tuberculous women

2 The extent of the tuberculous lesion seems to have no influence on the frequency with which this rise occurs

3 The rise in temperature varies from 1 29 degrees F in the moderately advanced cases to 1 41 degrees in the minimal and 1 6 degrees in the far advanced cases

4 The number of days before the menses are established that the rise begins is about nine days for all grades of tuberculosis

5 The rise in temperature lasts from 7 38 days in the far advanced cases to 8 81 days in patients with minimal tuberculosis

6 Church Street

BRONCHOMYCOSIS

REPORT OF TWO CASES *

WILLIAM ROYAL STOKES, M D †
BALTIMORE
EDGAR F KISER M D
INDIANAPOLIS
AND
WILLIAM H SMITH, M D
BALTIMORE

The etiologic relationship of certain forms of budding fungi included under the general name of *Endomyces* has been described by Castellani,[1] who in 1912 called attention to a number of chronic bronchial infections in Ceylon in which tubercle bacilli in the sputum were never demonstrated Such sputum, however, constantly contained various yeastlike organisms which he divided into several groups Later,[2] however, he enlarged this classification of the organisms that produced bronchomycosis, and in this paper he refers to certain bronchial infections in Ceylon caused by an organism known as *Monilia* This term, according to him, should include all the organisms of the family *Oosporaceae* Saccardo, 1886 The vegetative body of these organisms forms a mass of mycelial threads and free budding forms On culture mediums the old yeastlike forms are more numerous, while the mycelial threads or hyphae are very scarce or absent When present, they are short and narrow This family produces gas in various sugars, and Castellani's article contains a table showing the gas formation and reaction in milk of the genus *Monilia*

Certain monilias, such as *Monilia metalondinensis*, when injected into the lungs of rabbits in quantities of 1 cc of a slant agar growth, produced numerous white nodules in from fifteen to twenty days The microscopic examination showed a center composed of masses of small cells and polymorphonuclear leukocytes surrounded by a ring of phagocytes and endothelial cells and a few giant cells and eosinophils At times the center of the nodules was caseous Weigert s bacterial stain showed a small number of monilias

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[5] Butler Diagnostics of Internal Medicine ed 2 New York D Appleton & Co

[6] Caussimon J Clinical Value of Change of Temperature Curve During Menstruation in Tuberculous Women Presse med **37** 1557 1572 (Nov 30) 1929

* From the Bureau of Bacteriology Health Department, and the Franklin Square Hospital Baltimore and the practice of Dr Kiser Indianapolis

† *Dr Stokes died February 10*

[1] Castellani Aldo Lancet **1** 13 (Jan 6) 1912

[2] Castellani Aldo New Orleans M & S J **79** 21 (July) 1926

Clinically the disease may be either mild or severe In the former type there is no fever, expectoration is mucopurulent, physical examination shows only a few rales, and the condition may be cured spontaneously in from one to several months The mild condition may, however, turn into the severe type, which can also be present from the beginning The patient becomes emaciated, there is fever, the sputum is often blood-stained, and examination of the lungs may show areas of dulness, rales, and pleural friction sounds This type may terminate fatally

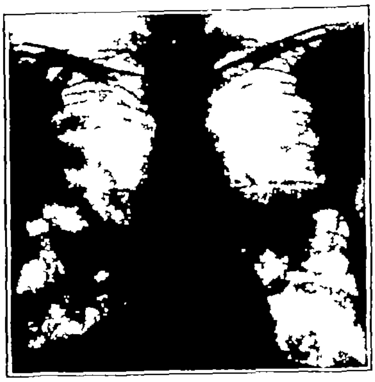

Fig 1 —Trunk markings and chronic interstitial fibrosis in case 1

The diagnosis is based on failure to demonstrate the tubercle bacillus and the constant determination of yeastlike bodies in the sputum These monilias can be cultivated by smearing some of the sputum over the slanted surface of Sabouraud's agar medium, and the special species may be detected by inoculating pure cultures of the organism into milk, gelatin and a number of carbohydrates The treatment consists in the use of potassium iodide, and autogenous vaccines are also said to be useful

Steinfield[3] isolated *Monilia* from cases of asthma and chronic bronchitis, and vaccines and potassium iodide treatment were beneficial to the patients De Potter[4] isolated *Monilia albicans* in a case of chronic bronchitis, and the organism produced a general mycosis in various laboratory animals Shaw[5] has also isolated a species, *Monilia richmandi,* from a case of bronchomycosis

Kotkis, Wachowiak and Fleisher[6] have found *Monilia* in the sputum in five of fourteen cases of bronchitis associated with asthma A table shows the acid and gas formation in a number of sugars, and the growth in milk and gelatin, but these authors made no attempt to recognize the various species Two of the patients showed improvement when treated by vaccines

Stovall and Greeley[7] report four cases of bronchomoniliosis in detail in which dyspnea on exertion, chills and fever, loss of weight, pulmonary dulness on percussion, bronchial breathing, cough, purulent and blood-stained expectoration, and anemia were all noted Roentgenograms showed peribronchial and pleural thickening, especially about the hilus, and the sputum contained typical yeast cells resembling *Monilia* This species was recognized by growth on the various culture mediums, and the organisms produced lesions in the experimental animals

McKinney[8] isolated twelve yeastlike strains from cultures from the sputum throat, mouth, stool and the pus of human beings Six of these strains proved pathogenic for guinea-pigs at times, three of them causing the death of the animals and the other three causing inflammatory reactions Immune serum was prepared from all of these strains, and each one of them agglutinated with the majority of the serums from the other heterologous strains They can therefore be roughly grouped under one immunologic classification, but when tested with an immune serum from commercial yeast with a titer of 5,120 these strains failed to agglutinate in any appreciable dilution with a serum made from the commercial yeast The commercial yeast also failed to agglutinate with the immune serums made from the pathogenic strains These pathogenic strains, therefore, can be separated as a distinct immunologic group from the commercial yeast strains

Gilbert and Groesbeck[9] have isolated strains of *Monilia* which were pathogenic for white rats from the sputum of eleven patients These patients often showed symptoms that suggested pulmonary tuberculosis, such as cough, fever and hemorrhages, but other conditions noted were chronic bronchitis, laryngitis and pulmonary abscess The cells isolated from the sputum were reproduced by budding, and short hyphae were often seen The cultures grew on agar and other routine mediums, and gas production was found in dextrose, saccharose, maltose and other sugars Intravenous inoculation was usually fatal to white rats in from one to five days, and the most characteristic lesion was the presence in the various viscera of foci of necrosis, with infiltration by mononuclear cells, and containing numerous colony-like masses of *Monilia*

On the basis of the literature that has been cited, the genus *Monilia* can therefore be described as an organism growing preferably on Sabouraud s agar, producing an abundant creamy growth with circular, creamy, smooth colonies elevated in the center These organisms are all gram-positive, oval cells, ranging in dimensions from 1 to 2 microns to 8 to 8 microns Some strains produce long hyphae, while in others the hyphae are short and narrow or absent Milk is usually rendered alkaline, gelatin is not liquefied, and there is acid and gas formation usually in glucose, levulose, maltose, galactose and sucrose, and occasionally in lactose and inulin Mannitol dulcitol, dextrose, raffinose, arabinose and xylose show no gas formation These species are usually pathogenic for such animals as guinea-pigs and rabbits, but are even more pathogenic for white rats They form a special immunologic group, as determined by agglutination and complement fixation tests, which separates them from the ordinary commercial yeast

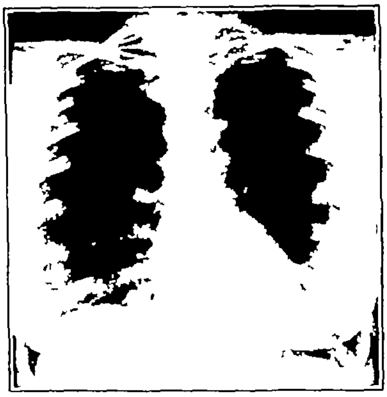

Fig 2 —Roentgenographic changes apparent in case 2

REPORT OF CASES

Case 1 —Our first patient studied was under the care of Dr Kiser

History —A white woman aged 33 complained of a harassing paroxysmal cough of several months duration and had lost 20 pounds (9 Kg) during the year This loss of weight and the increased metabolic rate noted on examination were probably due to an associated toxic adenoma of the thyroid gland

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[3] Steinfield E J Lab & Clin Med. 8 744 (Aug) 1923
[4] De Potter Compt. rend Soc. d biol 89:424 1923
[5] Shaw Science 64 300 1926
[6] Kotkis A J Wachowiak M and Fleisher M S Relation of Monilia to Infections of Upper Air Passages Arch Int Med. 38 217 (Aug) 1926
[7] Stovall W D and Greeley H P Bronchomycosis J A M A 91:1346 (Nov 3) 1928
[8] McKinney M J J Infect Dis 44:47 (Jan) 1929
[9] Gilbert and Groesbeck Am J Pub Health 20 1 (Jan) 1930

The symptoms worth noting in the physical examination were coarse, sibilant rales throughout the chest, but with a normal percussion note, roentgen examination showed rather heavy trunk markings with some extension of markings in the apexes Figure 1 shows to advantage the trunk markings and chronic interstitial fibrosis in this case

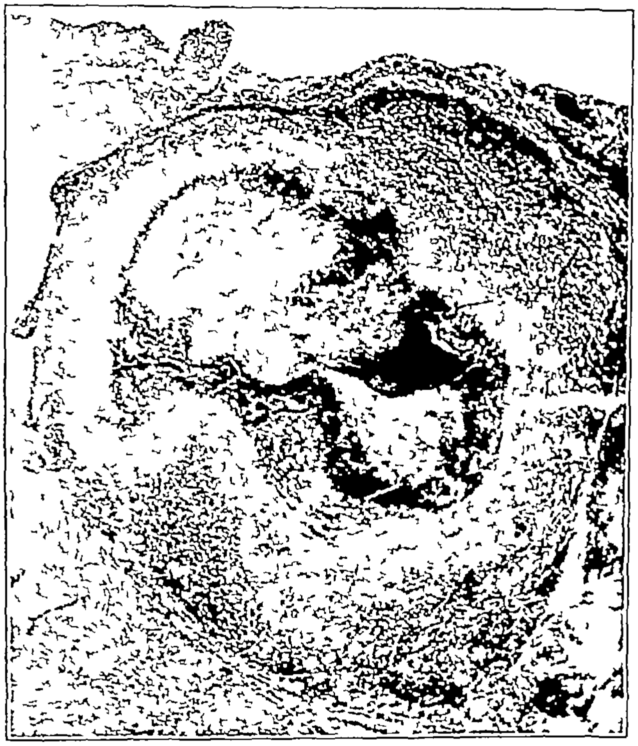

Fig 3 —Section of a pseudotubercle of the rat occurring just below the upper surface of the liver *The caseation nuclear fragmentation and the* epithelioid and lymphoid zones are well shown

Microscopic examination of the sputum showed many pus cells numerous streptococci and numerous budding yeast cells in repeated examinations in none of which was the tubercle bacillus detected The urine showed a trace of albumin, granular and hyaline casts and pus cells

Course—The basal metabolism increased from plus 5 to plus 52 in ten months The disease since has been uneventful the sputum showing decreasing numbers of yeast cells but at no time have they been entirely absent The blood counts were normal The cough has become less severe, and there has been no further loss of weight An observation made nearly two years after the first examination in this case showed that the cough was practically negligible and that there had been a marked improvement in the patient's general condition

Bacteriologic Examination—A pure culture of the yeast was obtained from the sputum, and the following characteristics were noted

Morphology The yeast when examined in the sputum consisted of round or oval cells frequently showing small buds varying in size with an average length of about 4 microns, the organism being gram-positive. In young cultures in Sabouraud's medium the morphology was similar to that described but in older cultures the cells became much more elongated often occurring in chains like linked sausages and at times forming structures resembling short hyphae The elongated ovoid forms ranged from 5 to 7 microns in length, whereas the hyphae varied from 10 to 15 microns in length These hyphae seemed to be growing directly from the mother cell as though they were elongated budding daughter cells

Cultural Characteristics The organism grew on agar and Sabouraud plates as large, moist, grayish white, convex, smooth edged colonies, and under the lower power of the microscope the colonies were coarsely granular They might be described as moruloid in appearance On agar slants there was a diffuse, moist, filiform growth Gelatin was not liquefied, the indole and the Voges-Proskauer tests were negative, and litmus milk remained neutral, but the reduction of nitrate to nitrite was positive

Fermentation Reactions Pure cultures of the organism were inoculated into arabinose, dextrin dextrose, dulcitol erythritol, galactose, glycerin, glycogen, inositol, inulin, lactose, levulose, maltose, mannitol, melezitose, raffinose, rhamnose, saccharose, salicin, sorbitol, trehalose and xylose, with the following results

From 20 to 40 per cent of gas was produced in dextrose, levulose and trehalose, while only large bubbles were produced in galactose, maltose, mannitol and melezitose

Animal Inoculations A white rat injected subcutaneously with 1 cc of the 10 cc washings of a Sabouraud slant agar tube was chloroformed and examined at autopsy one month later, and a pea-sized, yellow, soft, caseous area was found beneath the subcutaneous layer of the abdomen at the site of injection The various viscera were normal The yeast cells were recovered by cultures from the local area and stained sections showed that the mass consisted of connective tissue richly infiltrated with fibroblasts and containing areas of hemorrhage and many large pseudotubercles showing caseation nuclear fragmentation, epithelioid and lymphoid cells but no giant cells Another rat injected intraperitoneally when examined at autopsy one month later showed a pea-sized area near the umbilical region beneath the peritoneal surface extending through the abdominal muscles and surrounded by capsules of peritoneal and subcutaneous tissues The viscera were all normal The organism injected was recovered in pure culture from the local area, and microscopic examination showed a large conglomerate tubercle completely closed by muscular tissue and containing a central area of caseation with nuclear fragmentation and areas of calcification The capsule consisted of epithelioid, lymphoid and giant cells The kidney was intensely congested and hemorrhagic, the liver and spleen were congested and the submucosa tissue of the bronchi was extensively infiltrated by lymphocytes which produced a thickened area completely surrounding the lumen.

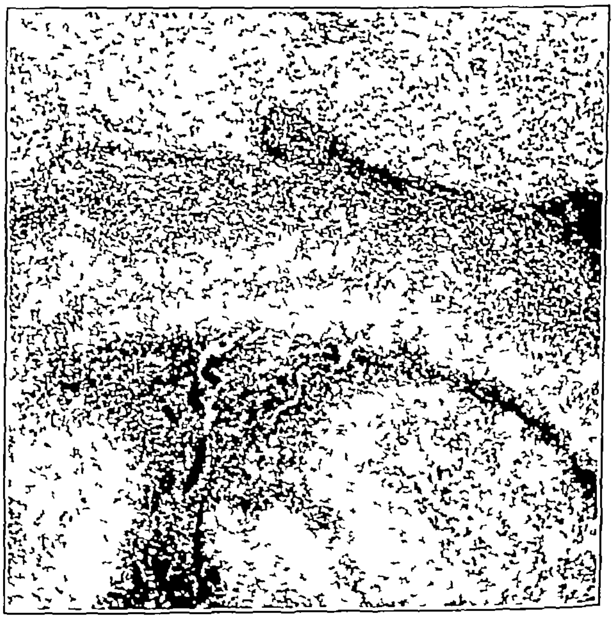

Fig 4 —Same section as in figure 3 under a higher power The caseation nuclear fragmentation loosely scattered epithelioid cells and the more densely packed zone of lymphoid cells are well shown together with the normal structure of the liver beyond the pseudotubercle.

Our second case was studied clinically by Dr Smith

Case 2—*History*—A man aged 45, in November, 1928 was seized with a cough and shortness of breath, the latter more pronounced on exertion He was often unable to lie flat at night, being propped up by pillows or resting in a rocking chair Expectoration of a yellow, sticky fluid had been considerable but there was no loss of weight, although night sweats had occurred Physical examination a month later showed harsh breathing, prolonged expiration, and wheezing throughout the chest and a few fine cracking rales posteriorly in both bases The percussion note was normal Roentgen examination of the chest showed marked infiltration involving the greater part of the right lung and also the center of the left lung There was very little infiltration in either apex. The lung changes were not characteristic and while they might have been due to tuberculosis, the possibility of some unusual condition such as syphilis or a fungus infection was kept in mind.

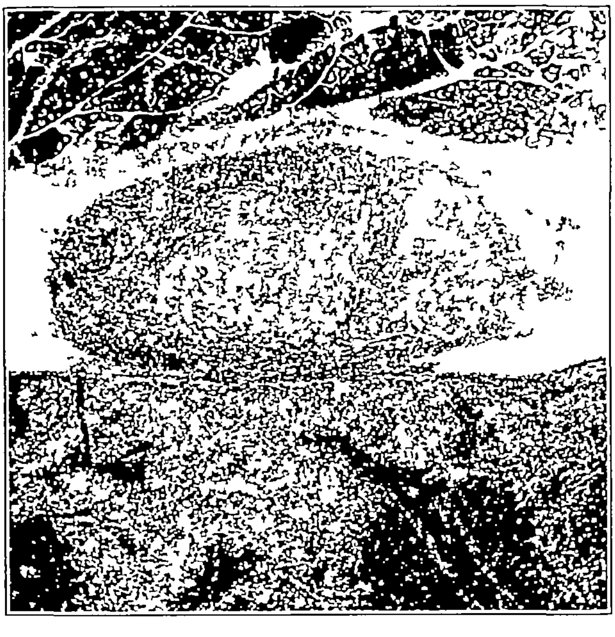

Fig 5—Section of a pseudotubercle on the peritoneal surface between the pancreas and the spleen The histologic picture is that of a tubercle produced by the tubercle bacillus with the central zone of epithelioid and giant cells and an outer zone of lymphoid cells

Examination of Sinuses—The frontal sinuses were normal There was rather marked clouding of the left antrum indicating the presence of pus or granulations, and slight clouding around the margins of the right antrum indicating either a cavity, which was well drained at this time, or a thickening of the lining membrane from an old infection All of the other sinuses were essentially normal Figure 2 shows the roentgenographic conditions apparent in this case

The condition remained about the same for several months when an autogenous vaccine was made from the yeast obtained from the sputum, which will be described later The concentration was 22,500 000 yeast cells per cubic centimeter and the first treatment consisted of a subcutaneous injection of 0 05 cc of the vaccine. No reaction being noted, the dose was increased by 0 05 cc every three days until 0.25 cc. was given After a four weeks interval the treatment was resumed by increasing the dose 0 1 cc every three days until 1 cc. was given By this time the patient seemed much better suffered less dyspnea and slept better After the 1 cc. dosage was reached nineteen more doses were administered at three day intervals with considerable further improvement The patient was then lost sight of and has not since returned for treatment

Organism Isolated—A number of microscopic and cultural examinations were made of the sputum in this case, and an organism was isolated repeatedly which corresponded in morphologic and cultural characteristics to the organism described in connection with the first case

Animal Inoculations—Intravenous injection of rabbits and intraperitoneal injection of guinea-pigs with washings of 1 cc. of the slant cultures were negative, but the white rat proved to be susceptible. One white rat given an intraperitoneal injection was chloroformed and examined at autopsy in a month, and a few pin-head sized light yellow, formed nodules were found scattered over the mesentery, the upper surface of the liver and the anterior walls of the stomach No invasion of the parenchyma of the organs was noted Cultures from the nodules yielded a pure growth of the yeast as already described Microscopic examination of sections of the pseudotubercles on the surface of the stomach, liver spleen, pancreas and mesentery showed essentially the same lesions, which were as follows

The central area of the pseudotubercles showed calcareous deposits nuclear fragmentation or caseation either alone or combined, and these areas were surrounded by a loosely woven zone of epithelioid cells containing occasional giant cells surrounded by a densely packed zone of small round lymphoid cells The lungs showed a few areas of intra-alveolar thickening

The second white rat injected at the root of the tail with 1 cc. of 5 cc. of the washings from a slant tube of Sabouraud agar was killed in a month, and the organs were normal on inspection Cultures, however, from the organs here described gave a pure growth of the yeast. The microscopic examination of sections showed that the liver contained a few small areas of focal necrosis consisting of a matrix of degenerated cells infiltrated by lymphoid and epithelioid cells and neutrophilic leukocytes There were extensive hemorrhages beneath the capsular surface of the liver In the lungs the tracheal submucosa was often greatly thickened by lymphocytes and the mucous membrane entirely or partially exfoliated, the lumen being filled with red blood cells, large and small lymphocytes and neutrophilic lymphocytes There was also great thickening of many of the intra-alveolar walls, and small tubercles consisting of lymphoid and epithelioid cells were scattered through the lung tissue. The spleen showed great congestion and large malpighian corpuscles The accompanying photomicrographs show these changes in detail

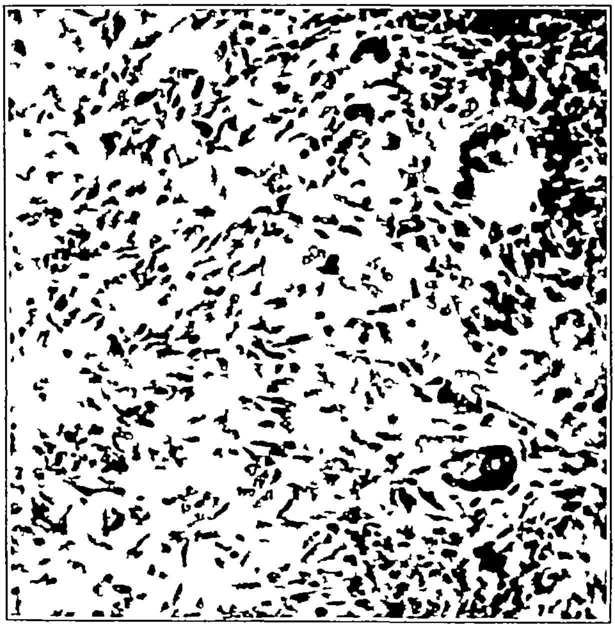

Fig 6—Section near the edge of the tubercle illustrated in figure 5 showing epithelioid giant and lymphoid cells

COMMENT

The interesting feature of these animal experiments consisted in the fact that we were able to produce tubercles resembling those produced by the tubercle bacillus, the only difference being that this organism itself was absent and that we were able to demonstrate the yeast bodies in sections and by cultures

SUMMARY

In two cases of extensive chronic interstitial fibrosis of the lungs the tubercle bacillus was not demonstrated in the sputum, but a form of yeast was obtained in both cases which in its morphology and cultural characteristics resembled *Monilia albicans* as given in Castellani's table,[10] with one exception, namely, in the liquefaction of gelatin and blood serum This organism when injected into white rats produced a pathologic condition similar to that produced by the tubercle bacillus but these lesions did not show any tendency to spread through the internal viscera and simply remained either as local processes or as scattered nodules on the serous surfaces

Classification of Fungi

Class	Subclass	Family	Genus and Species
Fungi	Fungi imperfecti	Oosporaceae	Genus Monilia Persoon Genus Oidium Link

Wallace and Tanner[11] isolated a specimen of yeast from sputum which resembles our organisms, even failing to liquefy gelatin, and as Castellani is quoted as saying that some authorities state that the organism liquefies gelatin, others affirm the reverse," we have classified our organism temporarily as *Monilia albicans*, since the cultural characteristics correspond to those of this organism in every other respect The isolation of these fungi from the sputum is, of course, no proof that they have produced the clinical conditions described here The repeated absence of tubercle bacilli and of other organisms, however, suggests an etiologic relationship The question can be finally settled only by a careful clinical study of cases as well as a thorough pathologic study of fatal cases It is probably true that many such cases escape observation, and a careful examination of the sputum should be made in all cases in which repeated examinations for the tubercle bacillus are negative

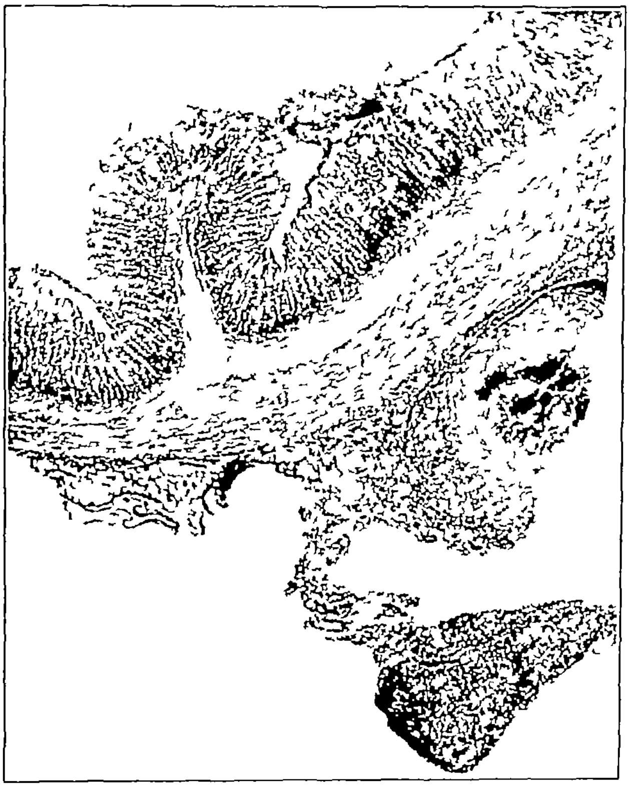

Fig 7 —A small pseudotubercle on the peritoneal surface of the stomach showing much central nuclear fragmentation and calcification

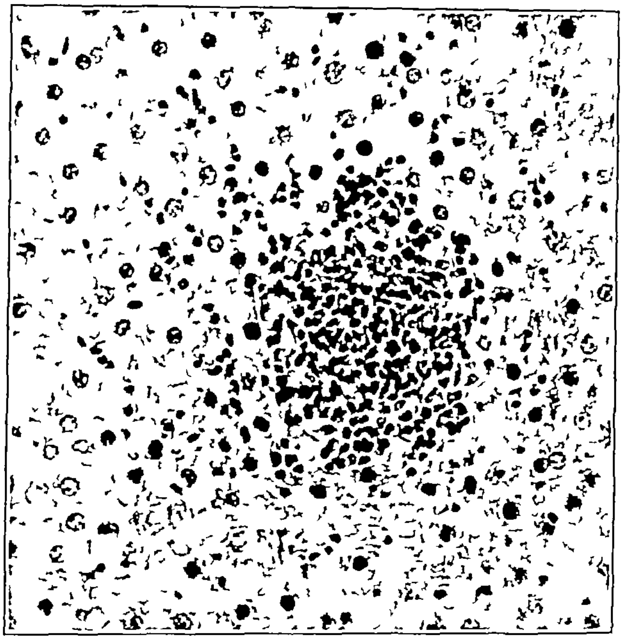

Fig 8 —A small pseudotubercle in the liver produced by injecting the yeast culture into a vein in the tail of the rat

Castellani's classification of the *Hyphomycetes, or Fungi imperfecti,* is presented in the accompanying table, and it can be seen that our organisms belong to this subclass, being of the genus *Monilia*

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[10] Castellani and Chambers Manual of Tropical Medicine ed 2 1913 p 822

[11] Wallace G I and Tanner F W Am Rev Tuberc 15 373 (March) 1927

Problems Involved in Prognosis—Prognosis, or forecasting what will happen, is a very important function of medical men, as it supplies what everyone is anxious to know when illness overtakes them or their relatives The power of predicting the duration and outcome of a given case of disease depends on several data first on accurate knowledge of the nature of the illness (diagnosis), secondly on knowledge of its natural history, course and significance, of the complications that may occur, the sequelae or results that may follow, and how far treatment can influence it beneficially, and thirdly on acquaintance with the individual patient s constitution, family history, inherited characters, mental traits, previous health and habits of life Prognosis thus involves problems all of which may not be capable of solution, particularly during the initial stages, and is probably the most difficult part of medicine It may be vitally important for a man with many responsibilities to know if he must face death at no long interval, and in these circumstances he should share the medical man s honest opinion but a fatal prognosis must be given only when there is absolute evidence In cases of doubt an optimistic view is better for all concerned, and even when there is every reason to anticipate the worst, the unasked warning may be harmful, and many patients know, though they do not really wish to be told, what is before them —Sir Humphrey Rolleston In 'Human Biology and Racial Welfare, Paul B Hoeber Inc New York, 1930

FRAGILITY AND DEFICIENT HEALING OF BONE IN POLIOMYELITIS *

I HARRISON TUMPEER, M D
AND
R W McNEALY, M D
CHICAGO

Antedating roentgen-ray assistance, Achard and Joffroy[1] described the bone changes in an extremity paralyzed by poliomyelitis In normal tissue they noted the projections of bone where the skeleton becomes continuous with the fibrous structures and deduced from this finding that the action of the muscles and the gliding of the tendons produce impressions and irregularities Therefore, they formulated the belief that the shape and structure of bone depends on its muscular connections In a paralyzed member, bone atrophy runs parallel with the muscle wasting and proceeds with modification in the size of the vessels of the region and the structure of the subcutaneous tissues In conditions of complete atrophy of muscle, it is easy to understand that the bone left in an inert mass of soft tissue is no longer subject to stresses and strains Consequently, it develops equally everywhere and takes an indifferent form The result is a smooth, glossy structure of uniform thickness The observers concluded that it was likely that the motor cell of the spinal cord exerted a trophic influence not only on the muscle of the region supplied but all of the tissue, including bone Following the introduction of the roentgen ray, Achard and Levi[2] reviewed the material and described the transparency of the bone, besides confirming the smaller diameters, thinned cortex and smoothness They then added that the texture and general morphology undergo change besides the change in the mass of the bone Since the diminution in length was less marked than the other changes, they established the fact that the process is a diaphyseal rather than an epiphyseal atrophy

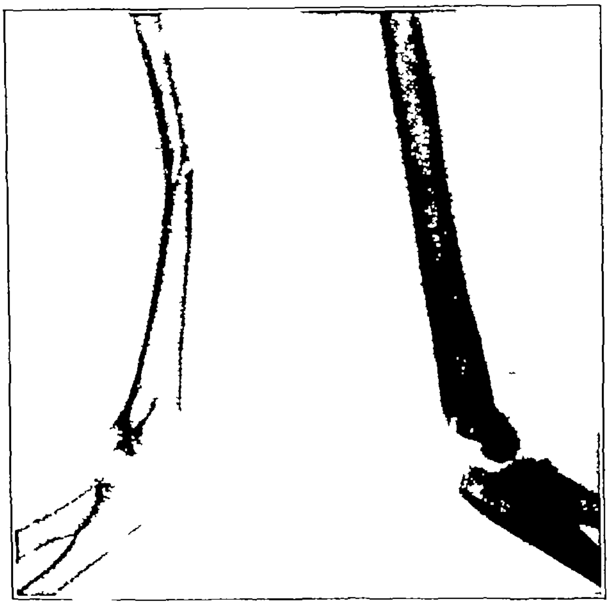

Fig 1 (case 1 Oct 18 1921) —Complete fracture of the right humerus at the middle of the shaft with some posterior angulation Note that the right humerus is considerably smaller than the left. Atrophy is indicated in the thin cortical layer the thin calcification of the medulla and the shadow thrown by the soft tissues The epiphyseal ends show less calcification because of the poor development of the muscles and their attachment

From these beginnings, the idea of bone atrophy accompanying nerve lesions was spread generally and soon appeared in the textbooks Oppenheim[3] remarks that there is a true atrophy in poliomyelitis as well as shortening, although more rarely the opposite condition, lengthening, may occur, according to Seeligmuller The latter regarded the changes as trophic, and even then this view was disputed Willard[4] mentions bone atrophy following the acute process of poliomyelitis Since that time reports have appeared by Hassin and his associates[5] describing changes in cases of thirty-seven and fifty-nine years' standing Their pictures agreed with earlier descriptions After comparison with the changes in a lesion of the lumbosacral plexus, these authors, too, conclude that the bone changes of poliomyelitis are characteristic for that specific disease This conclusion is open to objection, as will be seen further Of significance in their report is their opinion that regeneration must be meager, since growth, nutrition and function are impaired, and that healing may be slow or absent following trauma or other lesions

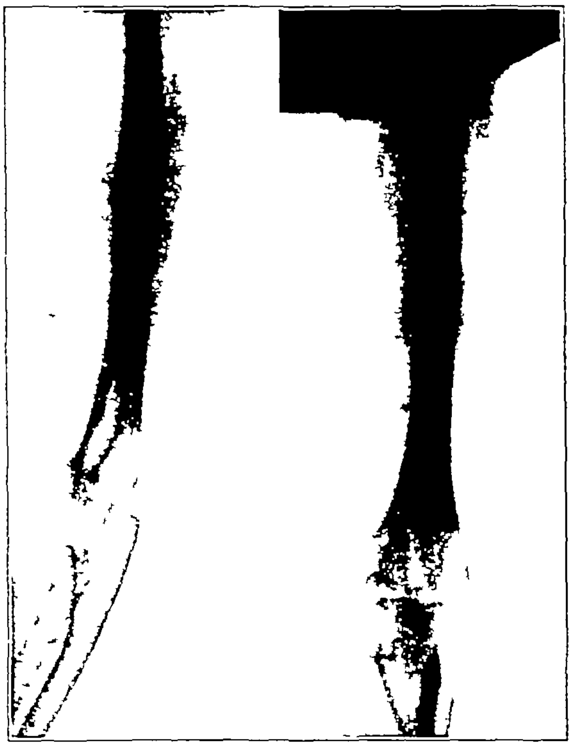

Fig 2 (case 1 Dec. 22 1921) —Refracture at point of old fracture. Contrast the two sides

With the increased interest in skeletal changes accompanying nerve disorders the question was raised, Are the bone changes due to trophic interference or are they simply the result of nonuse? Allison and Brooks[6]

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* From the Pediatric and Surgical Departments of the Post Graduate and Cook County Hospitals

[1] Achard and Joffroy Arch de med exper et d anat. **1** 57 1889

[2] Achard and Levi Nouv iconog de la Salpetriere **10** 324 1897

[3] Oppenheim Lehrbuch der Nervenkrankheiten Berlin S Karger 1908

[4] Willard Surgery of Childhood Philadelphia J B Lippincott Company 1910

[5] Hassin G B Lukas Christine and Brown R O Roentgenographic Bone Changes in a Case of Poliomyelitis J A M A **65** 1459 (Oct. 23) 1915 Hassin G B Baker E. I and Wakefield Howard Roentgenographic Bone Changes in a Second Case of Old Poliomyelitis ibid. **35** 267 (July 25) 192

[6] Allison Nathaniel and Brooks Barney Surg Gynec Obst **33** 250 (Sept.) 1921

conclude from their experimental studies that all the changes can be explained on the latter hypothesis The changes in the bones of animals after nonuse were the same whether the condition was effected by nerve paralysis, joint injuries or simple fixation in a plaster cast The atrophy was directly proportional to the degree of nonuse The changes were quantitative and not qualitative The effects were seen in size, shape, thickness, length, weight and texture, and accounted for the changes in gross anatomy, breaking strength and roentgenographic observations More interesting was the fact that regeneration was unaffected, so that a section removed from the paralyzed member was viable when transplanted to the normal extremity Allison and Brooks support their experimental observations with clinical data[7] They cite cases of poliomyelitis, fractures, osteomyelitis, nerve injuries, deformities and other conditions of nonuse Experimentally, the atrophic process begins in ten days It is well marked in ten or twelve weeks, and after from six to twelve months there is little further change Confirming these observations, Barbe[8] found rarefaction in the bones of the scapular girdle in a case of progressive muscular dystrophy which he stated seemed to be related to the muscular lesion at the scapular level On the other hand, in cases associated with unusual muscular tone, such as cases of Little's disease, Rohde[9] found changes indicating hypertrophy in six out of seven cases, in three of which changes were found in the bone as well as the joints He explains that the new formation occurs where the contracted muscles have broad and well vascularized attachments to the periosteum and bone

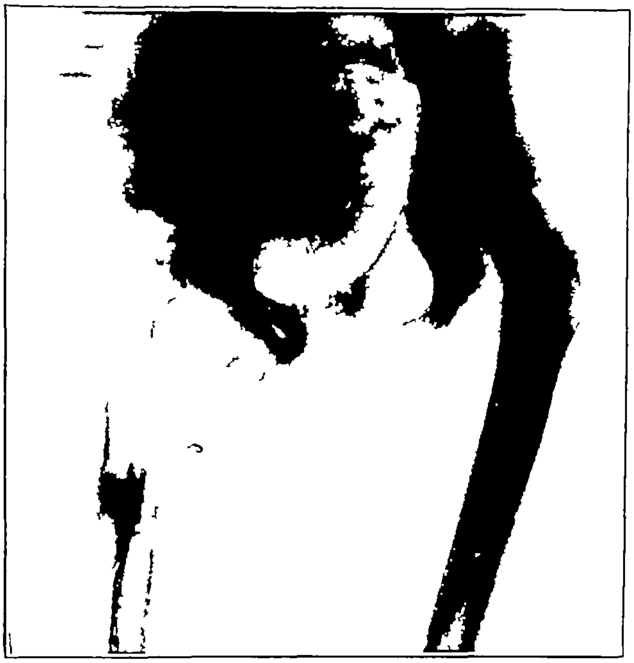

Fig 3 (case 2 Jan 14 1926)—Fracture of right femur showing median displacement dorsal of the distal fragment There is a limited probably inadequate callus Note the bone atrophy especially in the upper half

REPORT OF CASES

Case 1—This case is described because it involves several processes related to the poliomyelitic lesion namely, atrophy tendency to fracture and regeneration The patient was a girl, aged 5 years The circumstances of her admittance were interesting Her mother rushed up to the hospital desk with the excited pronouncement that the child had been thrown to the sidewalk by playmates and had broken her right arm The thought occurred to us that there must be a complete break with marked deformity since the mother recognized the condition Corollary to that conclusion, we decided that there must be some unusual factor to produce a complete noticeable break rather than a greenstick fracture in a young child Then the mother cried out that the fracture was in the bad arm A glance at the child explained the situation The child was robust, but the left arm dangled loosely and was thin compared with the right arm Poliomyelitis had occurred four years before. There was marked deformity, crepitus and abnormal mobility at the middle part of the upper arm The roentgen examination disclosed a complete fracture and the usual atrophic changes found in poliomyelitis The arm was placed in a splint, and healing took place. Two months later another fracture occurred at the same site following a minor trauma There was some backward displacement but no crepitus Fractures occurred repeatedly thereafter, and a roentgen examination was made eight months later, revealing good union morphologically Five years later the union was still effective, the child robust and the arm useless

Case 2—A boy, aged 10 years, was admitted to the Cook County Hospital with a fracture of the right femur following an automobile accident six weeks previously Six years before the child had had an attack of poliomyelitis affecting the right lower extremity According to the history a cast had been applied to the right leg and abdomen and traction had been exercised by means of adhesive strips extending half way up the leg, but when the cast was removed at six weeks there was no union Examination revealed atrophy of the right lower extremity from poliomyelitis Roentgen examination confirmed the presence of an ununited fracture at the junction of the upper and middle thirds of the right femur, with outward rotation and posterior displacement of the upper fragment Some callus was noted Buck s extension was applied and one month later there appeared to be firm union Roentgen examination at this time showed considerable callus but union was questionable. The patient could not extend the knee but he stated that he had been unable to extend the leg before the injury because of his disease Two months after his

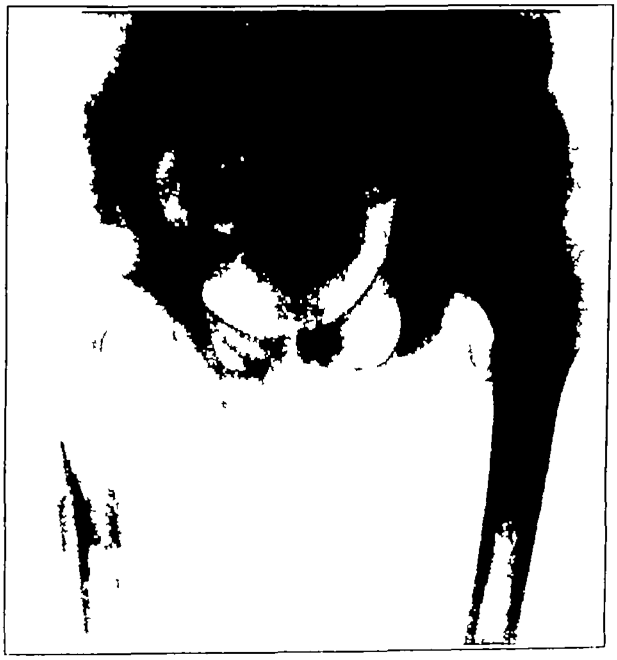

Fig 4 (case 2 Feb 5 1926)—The fracture shows a satisfactory alinement Note the sliver like transplant adjacent to the outer surface of the shaft.

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[7] Allison Nathaniel and Brooks Barney Bone Atrophy Arch Surg 5 499 (Nov) 1922

[8] Barbe A Rev neurol 35 201 (March) 1919

[9] Rohde C Munchen med Wchnschr 72 1874 (Oct. 30) 1925

admission and three and one-half months after the injury an inlay was made to strengthen the point of fracture. There was a marked osteoporosis and a relatively weak callus A graft from the normal left femur was placed into the right. A fragment of the affected right femur subjected to histologic examination did not reveal any unusual changes except atrophy Two weeks later the bone graft appeared to be attached by the callus

COMMENT

The bone changes in these cases are the result of two forces First, there is the atrophy accompanying poliomyelitis, whether trophic or because of nonuse Second, there is the growth process According to Allison and Brooks, the result of constant lack of function during the growth period is a relatively smaller and shorter bone

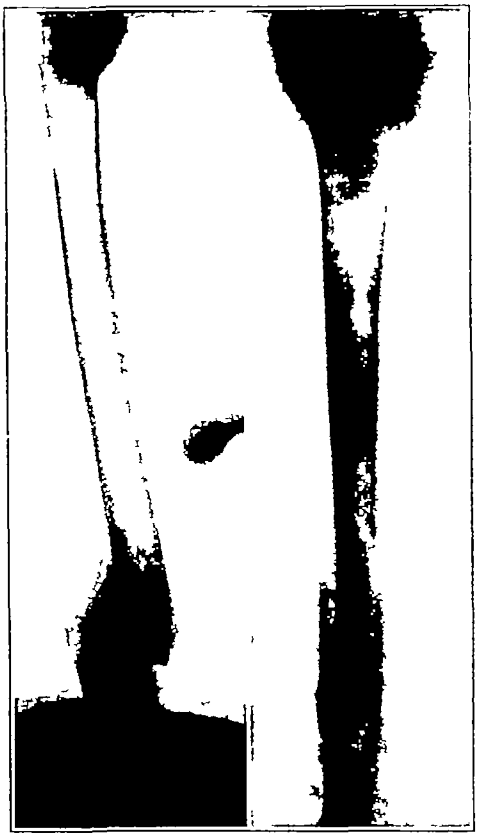

Fig 5 (case 2 Feb 16, 1926) —Fracture shows satisfactory alinement and complete dorsal position of the lower fragment There is a satisfactory but not abundant callus The tibial transplant is noted external to the fracture site.

The regenerative power of the bone is not affected by nerve lesions In these cases callus formation was present, indicating that regeneration does occur and confirming the observations of Allison and Brooks on this subject and of Putzu,[10] who found experimentally that nerve trunk lesions have no effect on the formation of callus There are complicating factors in these cases which must be considered, particularly illustrated in the first case namely absence of function and impaired nutrition due to the original disease In the first patient the affected extremity dangled uselessly In the second patient some functional stimulation was present from the activity of the gluteal muscles The importance of function is well known clinically and finds application in the modern treatment of fractures Wehner[11] confirmed experimentally the assumption that functional stimulus is the best means to promote the production of a callus This process can be traced in a series of roentgenograms The callus of functional encouragement is not merely a cement but in shape and structure is adapted to the use for which it is intended Although calluses in the cases reported here were developed repeatedly they did not develop the strength necessary to withstand even slight trauma because there was no functional stimulus

SUMMARY

1 Bone atrophy in poliomyelitis is indistinguishable from bone atrophy from nonuse

2 Atrophic bones are easily fractured

3 Callus formation occurs in the fractures of parts affected by poliomyelitis

4 Callus in such parts produces weak union because the functional stimulus is absent

310 South Michigan Avenue—30 North Michigan Avenue.

FETAL CEPHALOMETRY IN UTERO

A METHOD FOR ESTIMATING THE OCCIPITOFRONTAL DIAMETER, AND A STATISTICAL STUDY OF CEPHALIC MEASUREMENTS IN ONE HUNDRED AND FORTY-NINE UNMOLDED HEADS *

HERBERT THOMS MD
NEW HAVEN CONN

The importance of fetal cephalometry in utero becomes obvious when one considers the problems of suspected or real disproportion between the fetal head and the mother s pelvis Although it is possible by means of roentgen and other methods of pelvimetry to perform satisfactory mensuration of the maternal pelvis, it is universally conceded that at the present time a knowledge of the correct estimation of certain important diameters of the fetal head in utero is not available

In the present article a method is described which has proved satisfactory in my hands for measuring the occipitofrontal diameter in utero and a report is made of a statistical study of unmolded heads of new-born infants, in order to establish the relationship of the occipitofrontal diameter to other important cephalic measurements

The accompanying data are taken from the records of 149 infants delivered in the obstetric service of the Woman s Clinic of the Yale University School of Medicine The data represent a combined study of seventy-six infants born by breech presentation and seventy-three infants born by elective cesarean section In the breech series all cases represent infants born alive after easy extraction The presentation was persistently by the breech in this series except in those cases of second twin in which extraction was made by the breech In the cesarean section series all cases represent living infants from elective operations in cases in which the fetal head had not been exposed to the molding influence of labor

After a preliminary study of the data in which the records were considered in relation to the present study, it was decided to combine the two series and to make no sex differentiation With regard to the accuracy of the measurements, it may be stated that all infants were measured the day of birth, and in most cases this was done immediately following that event As to the accuracy of the observers, I may say in regard to the occipitofrontal circumference and diameter and the biparietal diameter that the mechanical error of determination is probably quite small, as in these measurements the end-points are definite bony landmarks

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[10] Putzu F Chir d org di movimento 5 393 (Aug) 1921 abstr J A M A 77 1274 (Oct 22) 1921

[11] Wehner E Beitr z klin Chir 123 541 1921

* From the Yale University School of Medicine and the obstetric service of the Woman s Clinic.

The importance of measuring unmolded heads has been emphasized especially by Scammon and Calkins,[1] who published their results in thirty-three infants thus studied Their average figures showed a distinct departure from measurements made some time after birth, and they comment "We think, however, that they approach more nearly the actual measurements of the full-term fetus in utero, since the cases upon which they have been based have not been subjected to molding, nor have they been increased by growth in the period between birth and the fourth day, when many of the published figures have been taken "

The accompanying tables represent the measurements of infants presenting unmolded heads at birth

Table 1—*Relationship of Occipitofrontal Diameter to Biparietal Diameter in One Hundred Forty-Seven Infants*

Occipitofrontal Diameter Cm	Number of Cases	Biparietal Diameter		
		Average Cm	Maximum Cm	Minimum Cm
13 00	2	10 00	10.50	9 50
12.75	1	10 25	10.25	10.25
12.50	14	9 90	11 00	9 00
12.25	8	9 60	10 00	9 00
12.00	33	9.50	10.25	9.25
11 75	3	9 40	9.50	8 00
11.50	28	9 40	10 00	8 50
11.25	4	9 20	9 75	8.00
11 00	27	9.20	10.50	8.50
10.50	7	8 00	9.50	8 00
10.25	5	8 90	10 00	8 00
10 00	11	8 40	9 00	7 00
9 00	4	7 40	8 00	5 50
8 75	1	5 50	5 50	6.50
8 50	1	6 50	6.50	6.50
8.00	2	6 70	7 00	6.30
7.50	1	6 30	6 30	
	147			

In table 1, it will be seen that in 117 instances, or 79 6 per cent, the occipitofrontal diameter falls between 10 5 and 12 5 cm, with an accompanying biparietal diameter of from 9 to 10 cm From the study of this table, it would appear that at least for unmolded heads in utero some modification of the sliding scale suggested by McDonald[2] is necessary for a working rule in estimating the biparietal diameter The following suggests itself

Given a measured occipitofrontal diameter of 12 5, substract 2.5 for biparietal

Given a measured occipitofrontal diameter of 12 0, subtract 2 5 for biparietal

Given a measured occipitofrontal diameter of 11 5 subtract 2 0 for biparietal

Given a measured occipitofrontal diameter of 11 0 subtract 1 75 for biparietal

Given a measured occipitofrontal diameter of 10 5 subtract 1 5 for biparietal

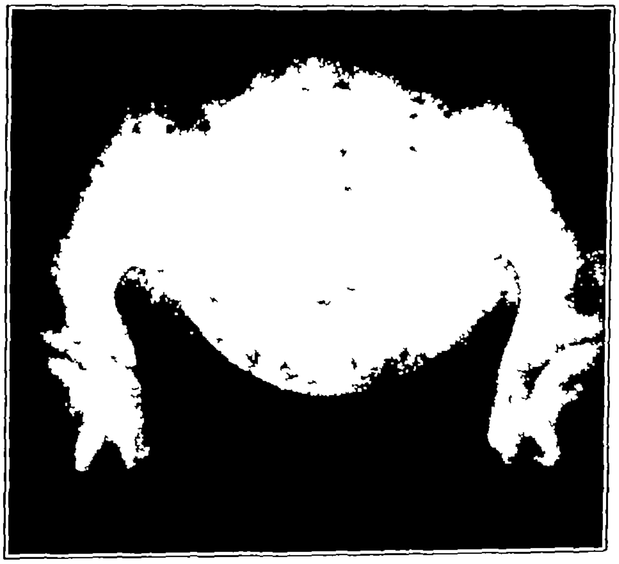
Given a measured occipitofrontal diameter of 10 0, subtract 1 5 for biparietal

Given a measured occipitofrontal diameter of 9 0, subtract 1 5 for biparietal.

The suboccipitobregmatic circumference (table 2) follows a definite ratio between itself and the occipitofrontal diameter It should be borne in mind that the measuring of this circumference in the living infant is probably subject to greater mechanical error of determination than the occipitofrontal circumference, because of the absence of definite bony landmarks from which the computation is made

Table 2—*Relationship of Occipitofrontal Diameter to Suboccipitobregmatic Circumference*

Occipitofrontal Diameter Cm	Number of Cases	Suboccipitobregmatic Circumference		
		Average Cm	Maximum Cm	Minimum Cm
13 00	2	35 75	37 00	34.50
12 75	1	33.50	33.50	33 50
12 50	14	33.70	36 00	31.50
12.25	3	32 60	33 00	32.50
12 00	33	32 40	36 00	27 00
11 75	4	31 40	32.50	30 00
11 50	28	31 90	34 00	29 75
11 25	5	30 40	31.50	29 00
11 00	28	31 40	31.50	27.50
10.50	6	30 40	31.25	26.50
10.25	4	28 90	31 50	28.00
10 00	11	28.50	32.00	27.50
9 00	4	26 00	27 00	25.50
8 75	1	23 00	23.00	23.00
8.50	1	24 50	24.50	24.50
8 00	2	22.00	23 00	21 00
7.50	1	22 00	22 00	22 00
	148			



Roentgenogram of the fetal head in utero The spaces between the dots represent square centimeters in the plane of the occipitofrontal diameter Not only is measurement of this diameter possible but an outline of the cranium may be made in its true proportion

A definite ratio is maintained between the occipitofrontal diameter and the circumference (table 3) It should be possible to construct some such working rule as that formulated on the basis of table 1 Table 3 demonstrates that in general the circumference is three times the diameter This appears to be a safe working rule for obstetric purposes

It has been fairly definitely established that the best index to fetal age is that of fetal length or crown heel distance (table 4) Reed[3] points out that babies put on weight in the uterus as easily and as variably as after birth Heaviness is a sign of present nutrition, while length is an indication of past assimilation Ballantyne[4] observes that "weight may not therefore be safely used as a solitary criterion of the length of antenatal life, at the same time the common sense of the matter must not be neglected Presence of excessive weight is not proof of postmaturity, for it may be due to other things, but its absence is prima facie evidence against the occurrence of prolonged pregnancy" Bossi[5] regards the weight of the fetus as of no importance in the diagnosis of postmaturity but places great reliance on the length in association with the development of the bones and the hardness of the skull

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[1] Scammon R E and Calkins L A The Development and Growth of the External Dimensions of the Human Body in the Fetal Period, Minneapolis 1929

[2] McDonald Ellice Mensuration of the Child in the Uterus with New Methods, J A M A 47: 1979 1983 (Dec 15) 1906

[3] Reed C B A Study of Fetal Maturity in Utero Surg Gynec Obst 25: 201 (Aug) 1917

TABLE 3—*Relationship of Occipitofrontal Diameter to Occipitofrontal Circumference*

Occipitofrontal Diameter, Cm	Number of Cases	Occipitofrontal Circumference		
		Average, Cm	Maximum, Cm	Minimum Cm
13.00	2	37.50	39.00	36.00
12.75	1	35.50	35.50	35.50
12.50	14	35.60	37.00	34.50
12.25	3	34.60	35.50	34.00
12.00	33	34.00	37.00	29.00
11.75	4	34.90	35.00	33.50
11.50	20	34.40	36.50	32.00
11.25	5	32.90	33.50	32.00
11.00	28	31.80	33.50	29.50
10.50	8	32.50	34.00	32.00
10.25	4	31.80	34.00	29.75
10.00	11	31.00	34.50	29.00
9.00	4	27.20	29.00	26.00
8.75	1	24.75	24.75	24.75
8.50	1	24.50	24.50	21.50
8.00	2	23.70	24.00	23.50
7.50	1	22.00	22.00	22.00
	148			

At the present time it is probable that the best procedure for obtaining the fetal length in utero is the Ahlfeld[6] method or the modification I described[7] in 1918 The latter procedure is particularly useful in those cases in which the fetal head lies low in the pelvis There are nevertheless certain conditions in which fetal length is difficult to estimate, as in individuals with thick abdominal walls and in certain cases of hydramnios In such instances it is apparent from table 4 that the estimate of the occipitofrontal diameter in utero not only is of immense importance when the pelvis is contracted but also is a valuable aid in establishing the age of the fetus From the data presented, it would appear that an intra-uterine occipitofrontal diameter of 11 5 or more would represent a safely mature child, while a child with a diameter of 11 0 cm would be but slightly, if at all, premature Infants with diameters under 10 5 cm would appear to be unquestionably premature

TABLE 4—*Relation of Fetal Length to Occipitofrontal Diameter*

Length Cm	Number of Cases Cases	Occipitofrontal Diameter		
		Average Cm	Maximum Cm	Minimum Cm
58.00	1	12.25	12.25	12.25
57.50	1	11.50	11.50	11.50
56.00	1	12.00	12.00	12.00
55.00	1	12.50	12.50	12.50
54.50	3	11.70	12.00	11.50
54.00	3	11.80	12.50	11.50
53.50	4	11.90	12.50	10.50
53.00	8	12.00	13.00	11.50
52.50	3	11.80	12.00	11.50
52.00	8	12.00	13.00	11.00
51.50	4	11.60	12.00	11.00
51.00	10	11.50	12.75	10.00
50.50	2	11.50	11.50	11.50
50.00	18	11.80	12.50	10.50
49.50	3	12.20	12.50	11.50
49.00	10	11.20	12.00	10.50
48.50	7	10.70	11.50	10.00
48.00	8	11.30	12.00	10.25
47.50	2	11.10	11.25	11.00
47.00	6	11.10	12.00	10.25
46.00	5	11.40	11.75	11.00
45.00	2	10.60	11.00	10.25
43.50	1	10.00	10.00	10.00
43.00	2	10.00	10.00	10.00
42.50	1	10.50	10.50	10.50
42.00	3	10.30	11.00	10.00
41.00	4	9.20	10.00	8.00
40.00	1	9.00	9.00	9.00
39.50	1	9.00	9.00	9.00
37.00	1	7.50	7.50	7.50
36.00	1	8.00	8.00	8.00
35.00	1	8.50	8.50	8.50
34.50	1	8.00	8.00	8.00
33.50	1	7.50	7.50	7.50

METHOD OF ESTIMATING OCCIPITOFRONTAL DIAMETER IN UTERO

My present procedure for estimating the occipitofrontal diameter in utero is essentially an adaptation of the method of roentgen pelvimetry[8] which has been developed in this clinic The plane to be measured must be identified and the distance above the sensitive plate measured This is performed by means of abdominal palpation and a pair of dividers In this connection it will be recalled that the two portions of the fetal body most easily identified at the end of pregnancy in the great majority of instances are the fetal forehead and the occiput. This is essentially true except in those cases in which at the end of pregnancy the head has already descended to a very low position in the pelvis In this instance the method is not as applicable, but it should be borne in mind that in such cases there is usually no question of disproportion and hence no pressing need for information concerning fetal head diameters In most cases in which the fetal head is riding above or at the brim, mensuration of the occipitofrontal diameter is possible and can be accurately performed

After the plane through which the occipitofrontal diameter passes has been established and the number of centimeters above the sensitive plate measured with the patient in the horizontal position, the exposure is made with the tube at a distance of 36 inches, centering directly over the midpoint of the diameter With the tube and exposed plate still in position, the patient is removed from the table and the perforated lead plate is introduced in the same plane as that occupied by the occipitofrontal diameter This plate is a 17 by 20 inch sheet of lead, 1 mm in thickness, mounted on a board and perforated with tiny holes just 1 cm apart A flash exposure is made on the previously exposed plate, and on development will be seen the image of the fetal head shadow and a series of black dots, farther apart than 1 cm, it is true, but representing the centimeter scale in the plane of the occipitofrontal diameter This corrects for at least a working basis the divergence of the rays in their passage from the target to the plate In viewing the developed plate, as shown in the accompanying illustration, it is obvious that not only may the occipitofrontal diameter be readily measured but an outline of the cranium may be easily drawn to scale This should be of importance in studying the effect of labor on the molding process of the infant head Such studies are now being made in this clinic

Questions will naturally arise with regard to certain points in the procedure outlined The first will concern the determination of the plane in which the occipitofrontal diameter lies After a little acquaintance with the method, it will be found that a considerable latitude in certain points is allowable For instance, the establishment of this plane within a range of from 1 to 3 cm above the plate affects the end-result so slightly as to be negligible for working purposes The question also arises as to the dipping of the vertex either anterior or posterior to the transverse diameter of the superior strait This also affects the end-result, but minimally, provided the head is not firmly fixed low in the pelvis

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[4] Ballantyne J W and Browne P J The Problems of Fetal Postmaturity and Prolongation of Pregnancy J Obst. & Gynec. Brit. Emp 29 177 1922.

[5] Bossi quoted by Ballantyne and Brown (footnote 4)

[6] Ahlfeld Bestimmungen der Grosse und des Alters der Frucht von der Geburt Arch f Gynak 2 1872

[7] Thoms Herbert A Modification of the Ahlfeld Method for Determining the Maturity of the Fetus in Utero, Surg Gynec. Obst. 26 563 565 (May) 1918.

[8] Thoms Herbert A New Method of Roentgen Pelvimetry, J A M. A. 92: 1515 1516 (May 4) 1929

In checking my results in infants measured in utero before, and extra utero immediately after, cesarean section, I have found that 2 mm should be added to the intra-uterine measurements This figure represents the thickness of the scalp over the frontal and occipital bones The shadow of this integument is not seen, of course, in the roentgenogram

SUMMARY

1 The average figures of the usual cephalic measurements of unmolded new-born infant heads show a departure from the measurements of molded heads

2 A comparison of the average figures for the various head diameters and circumferences shows a distinct ratio between the occipitofrontal diameter and the other diameters and circumferences

3 A knowledge of the occipitofrontal diameter in utero enables one to compute the biparietal diameter and the occipitofrontal circumference with sufficient accuracy for obstetric purposes

4 A knowledge of the occipitofrontal diameter in utero is of value in establishing the age of the fetus in utero

5 The method of roentgen fetometry here described makes it possible to measure the occipitofrontal diameter in utero

6 By means of the procedure here described, a profile of the cranium in utero is possible in its true proportions

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THE LEGEND OF THE PREVENTION OF MENTAL DISEASE*

I S WECHSLER M D
NEW YORK

The belief has become all too prevalent that a loud voice gives importance to ideas, that error sufficiently often repeated ultimately becomes truth, and that folly spread over wide regions somehow turns into wisdom Such is the nature of propaganda On more sober consideration, it becomes evident that the trumpet has no inherent virtues, that the radio imparts no fundamental attributes to ideas, that the printed word is endowed with no special magic, and that neither reiteration nor dissemination is capable of giving substance to a thought which is devoid of it Nevertheless, the popular mirage exists, and there is sufficient reason to suspect that science too, at least popular medical science, has been fascinated and has succumbed

Lest the title of this paper convey a wrong impression, let me make the trite observation that every physician, myself included, is firmly convinced that the future of medicine lies in scientific prevention But the loud fanfare about prevention has created the curious opinion that we are dealing with a modern concept or a modern discovery As a matter of fact, even the savage evolved what for him were definite methods of prevention That he made use of prayer, tabus, sacrifice, incantation and various sorceries does not alter the fact that by means of white magic he sought to prevent disease and actually believed that he did And in the field of mental disease he may even have attained some measure of success, the old wizard comparing not unfavorably with the modern cultist and quack, while the efficacy of the more ancient measures was neither greater nor less than many so confidently heralded in our own day

But the fundamental difference in the methods of prevention employed previously and some of the modern methods lies in the scientific recognition of causes It is by this standard—the knowledge of specific causes, of the mode of transmission and of the manner of evolution of disease—that we must test our ability to prevent, and it is by these criteria that I would test the claim so glibly and so confidently made as to the prevention of nervous and mental disease

Before proceeding, it may not be irrelevant to stress another fact, namely, that treatment, cure and prevention are entirely different matters There are diseases which we know how to prevent but not to cure, there are others which can be cured but not prevented, there are a few which can be prevented as well as cured, there are many which can neither be prevented nor cured, and, finally, there is that large group which can be treated but not cured

Sad as it is to make the confession, the fact remains that, despite accumulation of knowledge, the ultimate cause or causes of nervous and mental diseases is unknown There are a great many theories but few facts Their very profusion not only is in inverse ratio to our knowledge but is an actual confession of ignorance or merely a verbal cloak for it Nor do we know much about the role of heredity in the causation of illness and mental diseases, although admittedly it is a potent factor despite the loud claim of some that the superstition ought to be uprooted Nevertheless we see medical men issue in print or proclaim from the rostrum statements which cannot for a moment withstand the test of scientific investigation, we hear men state with assurance that they can prevent social and individual ills whose ultimate cause is utterly unknown, arousing false interest and vain hopes and enthroning themselves as popular idols in the guise of honest servants of accurate science

Enthusiastic mental hygiene tells us (and I am quoting from actual statements) that it is concerned with the prevention of mental deficiency, criminality, the psychoneuroses, the psychoses, antisocial traits, family unhappiness, divorce, prostitution, alcoholism, sexual perversion, epilepsy and other such simple matters All one can do is to gape and wonder or, perhaps, ask a few questions How much do we actually know of the causes of mental deficiency? Or to take the question of criminality, it admittedly depends on ill defined but undoubted hereditary factors, on mental deficiency, on diverse psychic and emotional states, on complex familial situations, on educational standards, on the social structure, on moral or ethical principles, on intricate matters of law and statutes, on politics, on concepts of justice, on religious views, and on a host of interrelated problems that will require generations to study, let alone to solve

Despite these elementary truths, endocrinologists do not hesitate to state that mental deficiency and criminality can be prevented by the simple process of juggling a few extracts of the glands of internal secretion I doubt whether it is an exaggeration to say that endocrinology is but a medical fledgling which has hardly emerged from the womb of experimental medicine and that it can be applied clinically with any degree of accuracy or success in but a few limited conditions Such is the uncertain, if not confused, domain of clinical endocrinology that one begins to suspect a recrudescence of alchemy And yet the claim is made that "glands" will cure and prevent and perform miracles No less modest are the claims of some mental hygienists

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* Abridged from a paper read at a joint meeting of the New York Neurological Society and the Section of Neurology and Psychiatry of the New York Academy of Medicine, Jan 14 1930

Without indulging in destructive criticism, one may ask, in all sincerity, What great advance has been made in psychiatry in the past twenty-five years, what new scientific discoveries have been made to warrant the sweeping generalizations and confident promises that mental diseases can be prevented? What do we know of the ultimate cause of dementia praecox? What do we know of the causes of organic psychoses that justifies boastfulness? What specific disease of the nervous system can we actually prevent? And have the psychoses diminished actually or relatively in recent years?

One enthusiastic exponent utters a repetitious formula, derived from a purely hypothetical notion, spun out of phantasy, without relation to clinical experience or laboratory facts, and explains, cures, prevents and promises all sorts of panaceas with—words All is so very simple inferiority accounts for neuroses, psychoses, perversions, criminality, greed, love, ambition, cowardice, bravery, poverty, alcoholism, marital infelicity, divorce, general morality, economic distress, wars, panics, revolutions, religion, history and philosophy, in short, every conceivable social and individual phenomenon A notion which does violence to all accumulated knowledge, which, if granted the dignity of critical analysis, is found to postulate the novel and evolution-defying concept that out of a biologic defect comes a biologic purpose, has been popularly accepted because it is easy, so simple that it requires no effort of thought for comprehension It is positively axiomatic and rests on the irrefutable evidence of—I say so

It is no discredit to psychiatry to acknowledge that it has barely emerged from the descriptive stage, that its practice is still considerably more of an art than a science, that it is perhaps less rooted in anatomy, physiology, pathology and all the laboratory sciences than most other branches of medicine. But instead of due regard for fact there is almost a groveling worship of formulas, an infatuation with fetishes of words New shibboleths are coined and the illusion is created that new facts have been discovered

One must also confess that what passes for social psychiatry is barely out of the religious or supernatural stage and quite deeply immersed in the speculative or metaphysical Sociology has not yet discarded medieval concepts, and scholasticism is not quite dead, nor is human thought altogether freed from the baneful influence which magic, religion and metaphysics have exerted on the development of the positive sciences We still speak of ultimate purposes and vital ends and call them by the high sounding name of teleology without recognizing that it is a religious and not a scientific concept

It is not my object to speak against the legitimate and well established efforts of prevention (I am purposely leaving out the important question of eugenics and its relation to mental deficiency and mental disease) I would not decry the honest but few achievements of mental hygiene in the study of mental problems, in the invaluable surveys of institutions for the insane and of prisons, in the establishment of child guidance and court clinics, in the humanizing efforts in the treatment of patients with mental diseases, in the focusing of attention on modern aspects of social psychiatry in the impetus it has given to the study of mental diseases inside and out of medical schools Nor would I overlook the fact that not only has the study of child psychology, based on sound psychoanalytic principles, resulted in valuable insight and moderate contributions but the dissemination of knowledge among physicians, parents and educators holds out considerable promise for the ultimate understanding of many of the problems of the neuroses

Without, therefore, impugning legitimate efforts and valuable results, I would still call attention to the sensational claims made in behalf of a budding science, and venture the opinion that much of the mental hygiene stock foisted on the lay as well as the medical public has been watered beyond reason and that it stands in urgent need of deflation I do not know of any other branch of science, not even excepting philosophy, which relies so much on words, so much on arm-chair thinking, and so little on accurate knowledge I do not know in what other fields speakers and writers say so much about so little, talk for hours on subjects which can be explained in minutes, issue volumes on what can be said in paragraphs, and succeed in giving the momentary impression that they have said something when in reality they have said nothing at all I am not aware of any other branch of learning in which future and painfully slow progress has been discounted in advance to such a degree and in such a great hurry

We have before us a shameful spectacle in the cancer prevention propaganda It is admitted, without exception, that we have absolutely no knowledge of the real cause of cancer and that we grope blindly in all our methods of treatment We employ the knife and radium and x-rays because we obtain some temporary and a few permanent results and because we know no better, and we are quite ignorant of the reason why, of two persons having apparently similar types of cancer in exactly or approximately the same parts of the body, one profits from treatment and the other does not But of true prevention or even control we know nothing Still that does not deter propagandists, and, to our shame be it said, also medical propagandists, from literally frightening people, even school children, out of their wits and making vain promises and arousing false hopes which are so often followed by tragic awakening Again I venture the opinion that, whatever the motive, science is not served thereby But to revert to my own topic, one shudders to contemplate that, since we already have fire prevention week and cancer week, we may soon read of criminal week, dementia praecox week, imbecile week, and what-not other week

I realize that much of what I have said, and perhaps the way in which it is said, will arouse stout resistance no less than vehement criticism For the crude way of expressing my thoughts I ask indulgence, for unintentional offense I wish to apologize If I have erred, I am open to conviction, if convinced, I am willing to retract My remarks have been animated solely by a desire to serve what I conceive to be scientific truth It is my opinion that progress is hindered rather than advanced by exaggerated claims, spectacular methods, and sham research Knowing how abysmal ignorance is, I feel that one should be extremely modest before knowledge One can pursue truth to greater advantage in silent retreats than in the noisy market place Useful discoveries can be well disseminated without the aid of trumpets The honest scientist does not announce his investigations before verifying his results To be a true scientist one must possess absolute intellectual integrity The great scholar not only is modest in his statements and constantly beset by doubts but can well afford the luxury of saying, "I do not know" Only the fool or the ignoramus deludes himself into thinking that he has taken out a patent on wisdom and a copyright on knowledge All of us still are children before the great unknown, and it ill befits us to play the role of high priests The day of omniscience, whether human or divine, is gone forever To insure progress we must honestly and courageously seek to avoid the dangerous paths of folly as well as the lurking pitfalls of error

1112 Park Avenue.

ERYSIPELOID

REPORT OF CASE OF INFECTION ACQUIRED FROM FISH OF GREAT LAKES *

EARL B RITCHIE, M D
AND
S WILLIAM BECKER, M D
CHICAGO

Erysipeloid is an acute inflammatory disease, starting in the skin, at times extending more deeply, producing cellulitis or lymphangitis and lymphadenopathy, sometimes accompanied by general symptoms It is due to an organism supposedly identical with that causing swine erysipelas (*Erysipelothrix suis*) The incubation period is two days, and the duration of the infection is from one to eight weeks The disease was reported from Europe as occurring after inoculation into a wound of decomposed animal matter, fish or cheese Reports in this country have been confined to the Atlantic seaboard (Gilchrist,[1] Klauder[2]), with the exception of Wile's[3] report of a similar condition in fishermen of the Great Lakes We have had the opportunity to study an unrecognized case of erysipeloid, and are reporting it to call attention to its presence about the Great Lakes and to record good results from the use of specific serum

REPORT OF CASE

A woman aged 28 seen Nov 23, 1929 complained of a painful eruption on the index and middle fingers of the right hand which had started five weeks previously as a fish-bone injury to the tip of the index finger She had purchased some fresh lake perch, already cleaned and scaled She recleaned the fish and injured her finger on a bone or spine (Inquiry at the fish market revealed that this market procures its fish from the Great Lakes It does not handle sea food and had never obtained fish from the Atlantic seaboard) Two days later she noted pain and tenderness and a sensation of burning at the site of injury A physician advised the application of heat. Five days later he incised the lesion but did not obtain purulent material Three days later the lesion had extended to the second interphalangeal joint, and the finger was erythematous, painful and hot. The lesion extended in a spiral course around the finger toward the palm. A second physician painted the lesion with sulphonated bitumen, applied an ointment containing sulphur and gave the patient a hypodermic injection in the thigh The process extended to involve a small area of the palm at the base of the index and middle fingers, and spread along the interdigital web up the middle finger These two fingers felt numb, especially at night.

The patient's past history was unimportant. On physical examination she appeared well nourished and of large stature. The thyroid was slightly enlarged No enlarged lymph nodes could be felt The blood pressure and the Kolmer Wassermann and Kahn precipitation reactions of the blood were normal

On the index and middle fingers of the right hand from the palm to the proximal interphalangeal joint were large dull red areas with irregular slightly elevated borders The areas previously involved appeared normal On the palm, extending about 2.5 cm from the base of the index and middle fingers, was an erythematous plaque, with no desquamation. The middle finger was swollen and tender, and just proximal to the first interphalangeal joint was an elevated, dusky red border

The patient was seen one week later, at which time the process had extended over the first interphalangeal joint of the middle finger Twenty-five cubic centimeters of *Erysipelothrix suis* serum (Mulford) was administered intragluteally A few hours after she had received the serum, she was nauseated and had diarrhea Two days later the lesion had extended slightly, although the finger was not so painful Five days after the administration of the serum an urticarial lesion developed at the site of injection, and the entire body surface was soon involved in urticaria This was accompanied by weakness, confining the patient to bed and stiffness and pain in the joints All symptoms slowly disappeared. Five days after she had received the serum, the fingers became normal and have remained so

COMMENT

Before the serum was given, 0 2 cc of sterile saline solution was injected into the advancing border of the lesion Material was aspirated, amounting to about 0 05 cc, and injected intraperitoneally into a white mouse At the end of three weeks the mouse was still alive and apparently normal It was killed and some of the heart blood was placed in brain hormone broth The medium remained sterile

Attempts by others (Gilchrist,[1] Bierbaum and Gottron,[4] Klauder[2]) to cultivate the organism by methods similar to ours were unsuccessful It is necessary to implant deeply excised tissue in the medium to obtain cultures This was not considered practicable in our case Specific serum has been used by Pick[5] and Klauder[2] with good results Pick treated some patients with normal horse serum, with no effect on the lesions He concluded from this that healing is not due to a nonspecific effect He was able to treat successfully cases of swine erysipelas and erysipeloid by means of specific serum, which he concluded is evidence of the identity of the two diseases

SUMMARY

A case of erysipeloid occurred following an injury from handling fresh fish from the Great Lakes The incubation period of two days and the course of the disease were typical Attempts to cultivate the organism failed The lesion healed in five days after the use of specific serum

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* From the Division of Dermatology Department of Medicine University of Chicago.

[1] Gilchrist T C Erysipeloid with a Record of 329 Cases of Which 323 Were Caused by Crab Bites or Lesions Produced by Crabs J Cutan Dis 22 507 1904

[2] Klauder J V Righter L. W and Harkins M J A Distinctive and Severe Form of Erysipeloid Among Fish Handlers Arch. Dermat & Syph. 14 662 (Dec.) 1926 Klauder J V Erysipeloid and Swine Erysipelas in Man J A. M A. 86 536 (Feb 20) 1926

[3] Wile, U J in discussion on Klauder Righter and Harkins (foot note 2) p 681

[4] Bierbaum K. and Gottron E Zur Kenntniss der Erysipeloids Rosenbach, unter besonderer Berucksichtigung seiner Beziehungen zum Schweinrotlauf Derm. Ztschr 57:5 1929

[5] Pick Erwin Zur Aetiologie und Therapie des Erysipeloids Dermat. Wchnschr 79:1627 (Dec. 20) 1924

INEFFICIENCY OF METAPHEN AS A SKIN DISINFECTANT *

EDWIN C. WHITE, PH D

AND

JUSTINA H HILL, M S

BALTIMORE

At least as early as 1908[1] the importance of eliminating the transfer of bacteriostatic amounts of drug to subcultures in making bactericidal tests of chemicals was emphasized In spite of this obvious and easily controlled source of error, one repeatedly finds in the literature reports of bactericidal action which on analysis turn out to be nothing more than demonstrations of antiseptic or inhibitory action By the addition of drug inhibition controls, it may be proved that in many such experiments sufficient chemical has been transferred to inhibit the growth of any living organisms that may have been carried over from the original test to the subculture

Another example of this error has recently appeared in the JOURNAL[2] Raiziss, Severac and Moetsch have reported that with solutions of metaphen, ranging in strength from 1 500 to 1 2,500, they obtained complete skin sterilization in every instance The "100 per cent" sterilizations were computed from three tests each with the 1 500 and 1 1,000 dilutions of drug, from two tests with the 1 2,000 dilution and from ten tests with the 1 2,500 dilution No drug inhibition controls were reported

Their technic was briefly as follows Shaved and cleaned rabbit skin was inoculated with heavy mixed cultures of *Staphylococcus aureus, Streptococcus hemolyticus* and *B subtilis* The inoculated area, a culture control from which was positive, was covered with sterile gauze saturated with the solution to be tested After five minutes the gauze was removed and at various intervals cultures were made by rubbing the test area with a moist sterile swab and dropping the swab into *"a test tube containing bouillon"* The volume of bouillon was not stated

In view of the high dilutions at which metaphen is said to have inhibitory action (Raiziss, Severac and Moetsch in their article state that it may inhibit the growth of *Staphylococcus aureus* in a dilution of 1 20,400,000), it seemed to us possible that the amounts of drug transferred to the "tube containing bouillon" might not have been diluted beyond an inhibitory concentration We therefore made the following drug inhibition controls Pieces of gauze saturated with 1 500 or 1 2,500 metaphen were applied to the undersurface of the forearm and allowed to remain in place for five minutes The gauze was then removed and by means of moist sterile swabs the centers of the treated areas were rubbed and the swabs dropped into test tubes containing bouillon Ten cubic centimeters of the medium was used in our tests The center areas rubbed covered not more than 1 square centimeter Tests in this way were made from (*a*) skin on which the drug had dried, (*b*) skin on which the drug had dried, with subsequent washing with a few cubic centimeters of sterile water, and (*c*) skin still moist with the drug In the series with metaphen 1 500, similar tests were made with transfers to flasks containing 900 cc of sterile broth, instead of to test tubes containing 10 cc These subcultures, both tubes and flasks, were then inoculated each with one 4 mm loopful of a twenty-four hour broth culture of *Staphylococcus aureus* Although the flasks showed a heavy growth of *Staphylococcus aureus,* as compared with a culture control, in no case did any of the ten transfers to 10 cc of bouillon in the 1 500 series show any growth In this series subcultures were made from skin still moist with the drug in two cases, from skin on which the drug had been allowed to dry in six cases, and from skin washed after the drug had dried in two cases In the parallel series in which 1 2,500 metaphen was used and allowed to dry on the skin before transfers were made to 10 cc of bouillon, seven of the tubes showed no growth of the inoculated organisms, *Staphylococcus aureus,* and three tubes showed a growth which was very scant in comparison with the control It is therefore conclusively shown that the tests of Raiziss and his co-workers with dilutions of from 1 500 to 1 2,500 of metaphen were invalid as bactericidal tests, because enough drug had been carried over to inhibit the growth of bacteria in every case

The Sterilization of Normal Human Skin with 1 500 Metaphen

Type Test	Total Number of Tests	Sterilized	Failed
Skin wet with drug not washed.	1	0	1
Skin wet with drug washed	7	2	5
Skin dried after drug not washed.	3	0	3
Skin dried after drug washed	3	3	0
	14	5	9

Having shown the invalidity of these metaphen tests, it became of interest to determine what value metaphen might have as a skin sterilizing agent when tested by a controlled method Areas of normal human skin of about 3 square inches and without any artificial contamination with bacterial cultures were covered with gauze saturated with 1 500 metaphen After five minutes' contact, the gauze was removed and an area of about 1 square inch in the center of each treated area was rubbed vigorously with a moist sterile swab until the skin became erythematous These swabs were then broken off aseptically and dropped into flasks containing 900 cc of sterile bouillon, which were incubated for seventy-two hours at 37 5 C Sterility controls were made of the swabs, of the bouillon used for moistening them and of the bouillon used for cultures The drug inhibition controls for these tests have already been described Skin controls from untreated areas were made for each series of tests and were invariably positive Areas of skin were studied in this way under four conditions (*a*) cultures made while the skin was still moist with the drug, (*b*) cultures made after the skin, still wet with drug, had been washed with a few cubic centimeters of sterile water, (*c*) cultures made after the drug had dried and without washing the skin and (*d*) cultures made after the drug had dried and the skin had subsequently been washed with a few cubic centimenters of sterile water It should be noted that those tests (*b* and *d*) in which washing was employed would be most favorable to the drug, because washing would help to remove any remaining bacteria from the surface of the skin The subjects were six members of the laboratory staff Two tests were made on the ankle, and all others on the underside of the forearm It was noted that in two cases in which sterilization was obtained, the skin control showed very light growth, which appeared only after forty-eight hours In all other cases the skin controls were positive in twenty-four hours

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* From the James Buchanan Brady Urological Institute Johns Hopkins Hospital

[1] Chick H J Hyg 8 92 1908

[2] Raiziss G W Severac Marie and Moetsch J C Metaphen J A M A. 94 1199 (April 19) 1930

These observations are summarized in the accompanying table

It is seen that in fourteen tests the skin was not sterilized in nine Apparent sterilization was obtained only in those cases in which the skin was washed with water after exposure to the drug, a procedure that may have washed away viable organisms, although its purpose was to wash away adherent drug We noted a variation in ease of sterilization among different skins The skin of one of the authors was sterilized in two tests The skins of two laboratory technicians were not sterilized in either of two tests on each individual

CONCLUSIONS

1 The recently published experiments of Raiziss, Severac and Moetsch showing that metaphen in strengths of from 1 500 to 1 2,500 invariably sterilizes inoculated rabbit skin are invalid because the amounts of drug transferred to the subcultures have been shown to be sufficient to inhibit bacterial growth

2 Metaphen 1 500, tested by a valid method, with exposure for five minutes and subsequent drying, cannot, according to our experience, be relied on regularly to sterilize normal human skin Different individuals show considerable variation in difficulty of sterilization

North Broadway

TUBERCULOUS PLEURISY*

GERALD B WEBB, M D
COLORADO SPRINGS, COLO

Pleuritic adhesions due to pneumonia have been demonstrated by Ruffer in Egyptian mummies Two typical examples of Pott's disease have been found on Egyptian monuments, and one marble statuette depicting the same disease was discovered These date from about 2000 B C, and belonging to the same period a mummy was discovered which, according to Sudhoff, undoubtedly presented evidence of Pott's disease Tubercle bacilli, however, have never been identified in Egyptian mummies, so it is not possible to prove that tuberculous pleurisy existed, even though tuberculous bone disease seems proved

Hippocrates advised hot water bottles, or bladders, and heat, for pain in the side Empyema was confused with tuberculous lung cavities, as is evidenced by Hippocrates' aphorism 44 "When empyema is treated by cautery or incision, if pure and white pus flow from the wound, the patients recover, but if mixed with blood, slimy and fetid, they die"

Aretaeus, who probably copied from Archigenes, in the first century of the Christian era described pleurisy thus "An acute pain accompanies it, which reaches to the throat, and in some to the back and shoulders, it is succeeded by a difficulty in breathing, nausea, redness of the cheeks, and a dry cough"

The first dawn of knowledge regarding tuberculous pleurisy came in 1805, when Bichat wrote "Pleurisies produce phthisis"

This observation followed Boerhaave's specific location of pleurisy in the pleura and not in the lung in 1730

Chapter V of Laënnec's immortal work on auscultation, published in 1819, contains much excellent information, pathologic and clinical, on pleurisy It is a curious omission, however, that Laënnec failed to describe the pleuritic rub, although Bichat, in 1805, had described the "bruit" which patients themselves heard or felt

Louis, about 1828, was an eager student of tuberculous pleurisy, and among other facts he noted that, in general, the larger the cavities found in tuberculous lungs, the greater was the area of pleuritic adhesions Trousseau, in 1843, advocated thoracentesis for pleuritic effusion Auenbrugger, in his studies on percussion, filled the pleura of a cadaver with fluid

The assertion that pleurisy was not due to cold or chill was made by See, who in 1886 wrote that tubercle was the etiologic factor, and this had been proved by Chauffard by the inoculation of guinea-pigs with small quantities of pleuritic effusions

But it is not until 1922 that the statement by Bezancon is found which it is my purpose in this paper to stress "At adolescence a pleurisy will often have revealed the impregnation of tubercle and it will only be a few years later that the pulmonary localization will manifest itself In some cases pulmonary disease will light up ten to twenty years later and subjects of pleurisy in youth may not become phthisic until mature or old age"

PATHOLOGY

Tuberculous pleurisy may be acute or chronic. The acute form may be dry—although Laënnec doubted whether pleurisy ever occurred without some effusion—or accompanied by a serofibrinous and, at times, hemorrhagic fluid Pleurisy with effusion can persist, occasionally, in spite of treatment, for a year or more The condition is not infrequently bilateral It is a frequent concomitant of artificial pneumothorax when the onset may be accompanied by a high and lasting fever in some patients

A dry pleurisy may be chronic and persist for years As we learn from autopsies, tuberculous pleurisy may result in widespread adhesions when the condition has been almost symptomless

Tuberculous pleurisy in general arises from a subpleural tubercle deposit, and the inflammatory condition is a result of allergy Following a pleurisy with effusion the original lung focus may, by roentgen study, seem to have disappeared

SYMPTOMS

Acute tuberculous pleurisy may arise insidiously in children and adults, without pain and at times without apparent fever

In the majority of patients, however, there is marked fever and definite pain Shakespeare, who may have experienced this condition, writes of "sidestitches which shall pen thy breath up" Huxley in 1887 had to forego engagements "by reason of a devil in the shape of muscular rheumatism of one side" Huxley experienced pain "the similitude thereof is a bird of prey periodically digging in his claws and stopping your breath in a playful way" Shelley was a victim of chronic pleurisy and experienced the weariness of the tuberculous, as is suggested by the following lines

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* Read before the annual meeting of the National Tuberculosis Association Memphis Tenn. May 8 1930

> I could lie down like a tired child,
> And weep away the life of care
> Which I have borne and yet must bear

In some patients, utter exhaustion may precede as well as follow pleurisy

Pleuritic pain may be present when no "rub" can be detected, and on the other hand a loud pleuritic "rub" can be heard, which may last a long time, and yet no pain may be experienced

Pain may be referred to the opposite lung, as noted by Laënnec The referred pains of diaphragmatic pleurisy, which occur in the shoulder and in the abdomen, are apt to lead to diagnostic errors The abdominal pains confuse surgeons and at times lead to unnecessary operations A simple test, and at times useful, which I suggested for diaphragmatic pleurisy, is to order the patient to lie on the affected side In such a position the recumbent diaphragm at first makes an increased excursion and this intensifies the pain of diaphragmatic pleurisy

In general, the symptoms of tuberculous pleurisy may simulate those of pulmonary tuberculosis, namely, a dry unproductive cough, malaise, fever, accelerated pulse and digestive disturbance The latter is at times most marked when pleurisy with effusion occurs on the left side

DIAGNOSIS

Judging by the large number of pleuritic adhesions found at autopsies, pleurisy must be overlooked often when it is present All chest pain and pain referred to the shoulders, arms and abdomen should lead a physician to suspect pleurisy Sometimes such pains may originate from diseased tonsils and teeth Cystic breasts in women, certain heart conditions, herpes zoster, gastric and spinal disease, and other possible causes may produce chest pains

Percussion is of great service in detecting change of resonance, and percussion with the tips of all four fingers should be used over the lung bases

Auscultation enables the physician to detect quiet breathing and the pleuritic rub I have described a method of auscultatory percussion which is of service in detecting pleuritic effusion Palpation of the trachea and of the position of the heart apex beat are important

Laënnec's egophony is of distinct value in detecting pleurisy with effusion Laënnec also called attention to the bulging of the side in pleurisy with effusion, and the retraction of the side which followed healing Laënnec noted the persistence of respiration along the spinal column in patients with effusion Good roentgenograms of the chest should always be taken and studied carefully Any difference in the lighting of the two sides should be noted and the pleural sinuses carefully compared Subpleural deposits are occasionally seen and definite parenchymatous lesions may be detected

TREATMENT

Rest, by means of strapping and posture, and heat, by means of an electric pad, are the best symptomatic methods of treatment

A patient who develops a tuberculous pleurisy should be given a long period of general rest, just as a patient with pulmonary tuberculosis, and the regimen should be continued for many months after all constitutional signs have ceased It may happen at times that a definite parenchymatous tuberculous lung lesion was present at the onset of the pleurisy, which became absorbed during the illness In these and other cases the roentgenograms taken after convalescence will lead physicians to be too optimistic regarding the future

There can be no doubt that many of the most malignant cases of pulmonary tuberculosis are in patients who give a history of pleurisy with effusion some years previous to their coming for treatment of pulmonary disease

The effusion that accompanies tuberculous pleurisy will usually be absorbed and paracentesis is not always necessary In some patients who present definite pulmonary lesions, the presence of the effusion may allow artificial pneumothorax to be undertaken With some patients it is exceedingly difficult to decide whether this procedure should be followed If the opportunity is neglected, the development of adhesions will prevent the operation, should the progress of the pulmonary process require it In a few patients I have succeeded in administering artificial pneumothorax when a history of completely reabsorbed pleurisy with effusion has been known This experience, however, is rare

Should extensive parenchymatous lung lesions be recognized, especially with cavitation, pneumothorax treatment should be instituted provided the opposite lung is sufficiently free from disease The tuberculous effusion may at times become purulent If uncomplicated by secondary organisms, repeated aspiration usually results in cure

COMMENT

Tuberculosis in any part of the body requires a long time for elimination or arrest Tuberculosis of the pleura originating in an apparently healthy individual should not be regarded lightly Two or three months of rest may bring about apparent cure, but actually from one to two or three years of a carefully regulated life is necessary in order to safeguard such patients against future pulmonary disease

A study that would seem worth while in pulmonary tuberculosis would be to ascertain the end-results in a large number of patients who have at some time suffered from tuberculous pleurisy with effusion

Allard and Koester noted that of 514 cases of pleurisy with effusion, no less than 47 7 per cent, in later years, developed pulmonary tuberculosis They also found a history of pleurisy in 650 out of 2,123 patients who developed tuberculosis

Lawrason Brown, in discussing the relative value of diagnostic data, places the history or presence of pleurisy with effusion first among five criteria

Marfan considered that subjects who had recovered from lupus or tuberculous glands were refractory to the development of pulmonary lesions

Similarly, tuberculous lesions in joints and bones appear to have value in preventing serious lung disease Possibly in some patients an attack of tuberculous pleurisy may render the lungs more immune

Theoretically, pleurisy, which is followed by adhesions, should render service by contributing to the "rest" of the organ, or possibly the reverse might happen

The general optimism, however, regarding the outcome of pleurisy with effusion is not justified and pleuritic disease should be regarded as seriously as pulmonary hemorrhage

402 Burns Building

Clinical Notes, Suggestions and New Instruments

COMPARATIVE EFFECT OF LIVER AND LIVER EXTRACT ON DIABETES IN A CASE OF COMBINED PERNICIOUS ANEMIA AND DIABETES *

Byron D Bowen M D Buffalo

This case is being reported primarily to record the comparative effect of whole liver and liver extract on diabetes in a case of combined pernicious anemia and diabetes It is, moreover, of some interest to add another case of this association to the seven already on record, as recently reported by Hitzrot [1] This combination of diseases is in all probability coincidental although they do have some possible predisposing points in common the majority of the cases of each occur at the same age period, both are more frequent in persons who are over weight, and the achylia gastrica that so frequently precedes pernicious anemia is rather common in diabetes, as was shown by Bowen and Aaron,[2] and later by others

In 1929, Blotner and Murphy [3] presented what appeared to be substantial evidence that raw liver pulp and a fraction of liver extract had definite blood sugar reducing properties This fraction was composed of insoluble fats, connective tissue and proteins, and was not effective in the treatment of pernicious anemia They also used the fraction that was effective in pernicious anemia but found that it had no effect on the blood sugar They felt that 180 Gm of raw liver pulp was equal to about 10 or 15 units of insulin, these impressions were gained by the use of tolerance tests and by repeated observations on several well standardized diabetic patients over a long period Murlin, Pierce and Gregg [4] state that the insulin content of fresh liver may be the explanation for these results

CLINICAL HISTORY

A man, aged 55, developed anemia in September, 1928 He improved after the use of liver and liver extract In March, 1929, diabetic symptoms appeared and his weight dropped from 155 to 127 pounds (from 70.3 to 57 6 Kg) in a short time When I saw him in May, he had been taking 15 units of insulin daily for only a few days and he had had no liver for five weeks His maximum weight had been 185 pounds (84 Kg) in 1927 It had always been his habit to eat liver once a week.

Physical examination showed advanced pyorrhea about the remaining lower teeth The spleen was not palpable and there was no evidence of involvement of the central nervous system

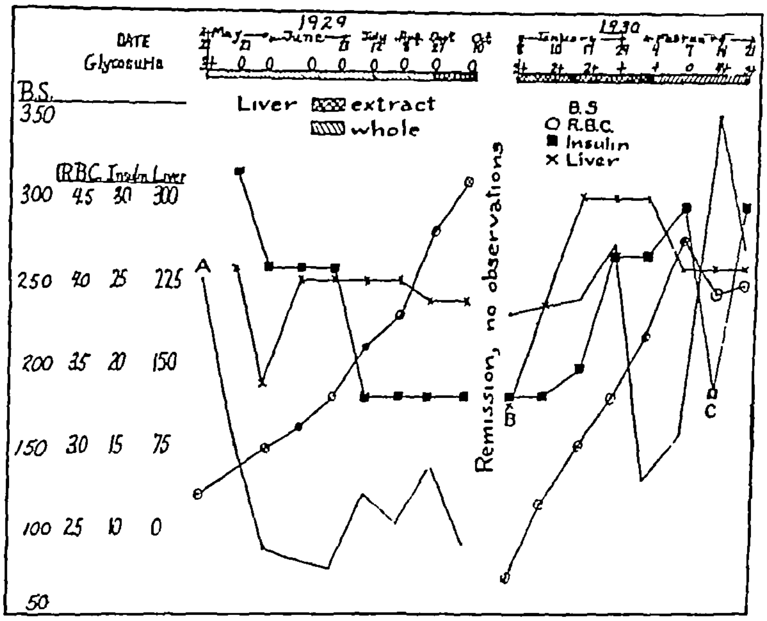
Achylia gastrica was present. The blood was typical in all respects of pernicious anemia The hemoglobin was 50 per cent The quantitative van den Bergh reaction was 1 82 units The urine contained a large amount of sugar but no diacetic acid The blood sugar was 304 mg during digestion He was given a diabetic diet containing 80 Gm of carbohydrate, 100 Gm of protein and 120 Gm of fat He received about 200 Gm of liver daily, one half of which was raw pulp He was not observed in the hospital, but his diet and insulin dosage were carefully taught to him

RESULTS OF OBSERVATIONS

With the exception of the first blood sugar test, all observations were made between noon and 1 o'clock

First Period (from May 22 to Oct 10, 1929)—There was a prompt recession of the diabetes with the use of whole liver and insulin The insulin dosage had to be reduced to 18 units daily because of hypoglycemia Liver extract was substituted for whole liver after the blood count approached normal, from September 27 to October 10 During this time there was no essential change in the diabetes

Second Period (from Oct 10, 1929, to Jan 8, 1930)—During this time there was considerable remission of both the anemia and the diabetes The patient was not under observation The patient took liver very irregularly, but he had had 120 Gm. daily for ten days prior to the tests made January 8 Insulin, 18 units daily, was continued throughout the period The patient stated that he had kept strictly to his diabetic regimen except for a slight infraction of diet during the holidays He found sugar in his urine shortly before he was seen in January, but he admitted that he did not make frequent examinations



Record of blood sugar in a patient on a diabetic diet and receiving liver and liver extract *A* fasting *B* for ten days *C* insulin reduced three days before this test

Third Period (from January 8 to February 14)—This was the second period of observation The anemia was first treated with liver extract, during which time the insulin dosage had to be nearly doubled, which suggested that the whole liver had been effective in lowering the blood sugar during the first observation period February 4, however, at a point when both the diabetes and the anemia were well under control, whole liver cooked and raw, 80 Gm a meal, was substituted for the extract. There was no further lowering of the blood sugar and no insulin reactions Three days prior to the last observation on February 14, the insulin was sharply reduced 10 units, bringing the dosage back to a point which had controlled the diabetes during August, September and October The blood sugar, however, was found to be 350 mg, and the urine contained a 4 plus sugar reaction in all specimens during the twenty-four hours Insulin was then increased to 28 units, a week later the blood sugar was 263 mg and the urine contained a 3 plus sugar reaction

SUMMARY

No evidence of a blood sugar lowering action of liver was found in the case of combined diabetes and pernicious anemia here reported The diabetes in this case became more severe during the two month period that the patient was not under observation

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* From the Buffalo General Hospital and the University of Buffalo School of Medicine

[1] Hitzrot L H Coincident Diabetes Mellitus and Pernicious Anemia Am. J M Sc. 177 213 (Feb.) 1929

[2] Bowen B D and Aaron, A H Diabetes and Gastric Secretion Arch Int. Med. 37 674 (May) 1926

[3] Blotner Harry and Murphy W P The Effect of Liver on the Blood Sugar Level J A. M A 92: 1332 (April 20) 1929

[4] Murlin J R Pierce H B and Gregg D E The Relation of the Liver to the Action of Insulin, Am. J Physiol 90 458 (Oct.) 1929

Council on Physical Therapy

The Council on Physical Therapy of the American Medical Association has approved the following article.

H J Holmquest Secretary

THE REHABILITATION OF THE DISABLED

HARRY E. MOCK, M D
Chairman of the Council on Physical Therapy of the American Medical Association
CHICAGO

During the last two or three decades, a new era in the practice of medicine has gradually developed This is frequently referred to as the era of physiologic medicine, of physiologic surgery Great stress will always be laid on the need of diagnosis before adequate treatment can begin, on the importance of clear knowledge in pathology before adequate diagnosis can be made, and on the value of therapeutic and surgical methods But greater and greater emphasis is being placed on the need of viewing the results of treatment from a physiologic point of view, that is, the prevention of abnormal states and the restoration of function in diseased organs or members to as near normal as is humanly possible

From a surgical standpoint such physiologic results cannot be obtained if the surgeon is content with the immediate surgical end-result, if he loses interest in the follow-up of the case before he is assured that the functional result has been attained Healing the burns and then leaving the patient to his own devices to overcome the scar contractures is not adequate treatment The best possible reduction of the fractured leg and treatment until solid union has occurred is poor surgery if meanwhile the surgeon has paid no attention to the protection of adjacent joints, has given no consideration to maintaining muscle tone, and fails to utilize those adjuncts of treatment which will assure a rapid return to normal function of the injured leg

Only by the continued interest of the physician in his patient during the long period of chronicity of the disease or injury, during the long days of convalescence, even following the patient back on the job to ascertain that proper work is secured or assigned to him and making sure that both his mental and physical restoration is assured can the ideals of physiologic medicine be achieved

Definite knowledge of those remote and so often neglected therapeutic regions which lie beyond the therapeusis of the acute stage of disease and injury are necessary In these regions are found the provisions for physical therapy, occupational therapy, suitable convalescent care, placement at proper employment and often retraining for new work when the injury or disease has made return to the old job impossible A sympathetic understanding of these provisions and sufficient knowledge to utilize them is absolutely essential for the attainment of this ideal of modern medicine—the rehabilitation of the disabled

The field and scope of rehabilitation of the disabled lead the physician to consider many lay adjuncts that heretofore have never been considered a part of medicine But to accomplish successfully the rehabilitation of patients the profession must make contacts with these lay agencies

Rehabilitation includes

A Prevention
1 By analytic study of the disease or accident to prevent a similar occurrence to other individuals
2 By treating the case in such a manner that function will be preserved in adjacent parts, that traumatic neuroses will be combated from the start, that habits of idleness and loafing will be prevented.

B Treatment
1 The best possible treatment directed toward the earliest possible recovery with the greatest possible functional restoration
2 The use of physical therapy as an aid in functional preservation and restoration
3 The use of occupational therapy to combat habits of idleness and often for the purpose of retraining for new work.

C Convalescent care
1 The early removal of the patient from hospitalizing influences
2 Seeking convalescent provisions for those who room and board or whose home conditions furnish unsuitable convalescent environment.

D Placement at suitable employment
1 Light occupations in the industry until such a time as the patient can return to his regular position
2 Choosing a suitable job when disability prevents return to his old position
3 Development of placement bureaus for the handicapped

E Training for a new vocation when disability unfits for the usual occupation
1 Cooperation with state vocational training bureaus
2 Work for the shut-in

F Medical follow-up to see that rehabilitation is completed and so remains

PREVENTION

The short report blanks furnished by most insurance companies for the reporting of injuries are inadequate for a careful analytic report of the cause of the accident from the surgeon's point of view Often, in securing the history of the case, the surgeon gains valuable information concerning the cause of the accident or the immediate handling of the case at the plant which, if transmitted to the proper authority, may prevent recurrences of similar accidents

Example—Mr B was admitted to the hospital with several fractured ribs the result of a small hoisting machine falling over and striking him in the chest. He told the surgeon that this machine was old and insecurely fastened and that he had complained about it but that nothing was done. Report of these facts to the personnel office at the given plant resulted in correcting similar conditions in several of these small hoisting machines, thereby preventing future accidents

Every physician or surgeon today engaged in private or hospital practice secures information from certain patients that shows a work hazard as responsible for a given condition A short letter stating the facts to the responsible industry will in most instances result in a correction of the condition and therefore the prevention of a similar disease or accident This type of prevention work is just as essential as the reporting of contagious diseases or of lead poisoning, yet how few physicians think of this as a duty ?

Almost every surgeon knows that a wrist drop should be combated from the start by the use of a cock-up splint, that a foot allowed to hang downward in the position of foot drop for even a few weeks will mean a prolonged disability case and often a permanent disability, that a shoulder joint injury treated for any length of time by strapping the arm tightly to the body or by even carrying the arm in a sling usually means inability to abduct or elevate the arm for weeks or months after the original injury is healed, or that prolonged immobilization of a limb in a circular cast without any opportunity for massage of the muscles or very limited exercise of the adjacent joints means weeks and months of unnecessary treatments to overcome conditions that could have been prevented

Hardly a week goes by that a case of this nature is not referred for reconstructive surgery A surgeon must be "rehabilitation conscious" at all times if he is to prevent these concurrent disabilities

TREATMENT

To the surgeon interested in rehabilitation will be referred in the course of time many patients in dire need of reconstructive surgery Deformities and handicaps must be corrected and function restored as far as is humanly possible before the subsequent steps of rehabilitation can be completed This is becoming so well recognized that state departments of vocational reeducation for the disabled, state compensation boards, schools interested in the training and education of crippled children, industries and railroads and even private organizations interested in the disabled are frequently sending patients to these surgeons to ascertain whether anything can be done to improve their physical handicaps

This type of surgery is often referred to as physical rehabilitation Too often it is apparent to the reconstructive surgeon that if proper measures had been instituted during the initial treatment this subsequent physical rehabilitation would not be necessary

Examples—Ununited fractures make up a large percentage of these reconstructive cases There are many of these in which the cause of nonunion cannot be ascertained In others the commonest causes are, first, repeated efforts at reduction in order to secure a good roentgenographic result, that is, to show the fragments almost perfectly alined, and, second, the open treatment of fractures with the application of some foreign material as an internal splint, usually a plate

The best example of repeated attempts at reduction occurs in fractures of both bones of the forearm It is extremely difficult to secure end to end apposition of the fragments in both bones Repeated and repeated efforts only tend to cause nonunion A fair apposition of these fragments will in nearly every instance give an excellent functional result But surgeons are afraid to present before industrial boards even good functional results when the roentgenogram shows very poor alinement of the fractured fragments This attitude will not change until surgeons educate and hammer into the heads of commissioners of industrial boards and of lawyers that what we are seeking is good *function* and not beautiful x-ray pictures

Approximately 33⅓ per cent of all fracture cases referred to me for nonunion have previously undergone operation In nearly every instance a plate or other foreign material has been used in an attempt to hold and secure union Cunningham of Oklahoma City, the surgeon used frequently by the state industrial commission for reconstructive surgery, states that he has a bucketful of these plates removed in nonunion cases I recognize that in the hands of many excellent, thoroughly trained surgeons, this method may prove almost perfect but from my experiences and observations the great majority of surgeons cannot use them successfully

Deformities of the hands following tendon and nerve injuries contribute largely to reconstructive surgery In many of these cases the original operations by the surgeon treating the initial injury would have been successful if that surgeon had been familiar with and had had the facilities for administering proper physical therapy Quite frequently I find no operative procedure necessary in such cases but simply refer them to the physical therapy department for physical rehabilitation methods

The stiff shoulder joint following treatment for dislocation or fractures in and about the upper end of the humerus, bursitis and traumatic arthritis make up a very high percentage of cases referred for reconstructive treatment In the majority of these cases if the initial treatment had been aimed at the protection of the weak group of muscles, the abductors and external rotators, the subsequent reference of the case would never have been necessary Treating the acute injuries about the shoulder joint with the arm abducted and elevated—the airplane splint position—and the use of early heat and massage to the part would eliminate many cases of permanent handicap

Breaking up the stiff joint by manipulation under anesthesia results in many permanent, bony ankyloses This is especially true when such manipulative treatment is applied to the elbow joint The slower methods of physical therapy are far better

In a certain number of skull fractures, the syndrome of persistent cerebral contusion develops Too often these sufferers from indefinite symptoms are called malingerers and are mishandled for months or even years They make up a pitiful class of the handicapped for whom rehabilitation is very difficult

The same is true of many back injuries inadequately diagnosed and therefore inadequately treated during the acute injury I have had six cases of compression fractures of the vertebrae referred to me during the last two years, months after the injury had occurred, which had gone undiagnosed simply because a lateral roentgenogram had not been made Every one of these patients was handicapped and in need of rehabilitation

PHYSICAL THERAPY

No surgeon today is adequately equipped to treat trauma cases who is not familiar with those physical therapy measures which will assist in restoration of function It is not necessary for him actually to administer the physical therapy, but he must know when massage and active exercise should start in every type of fracture, when heat, massage and muscle training exercises are indicated in nerve and tendon injuries, when heat in the nature of diathermy is indicated

Manufacturers of certain forms of machine therapy, for example, lights and electrical apparatus, have been active in advertising and selling these agents to the profession until many surgeons think that physical therapy refers only to such modalities They have their uses in the hands of specialists in physical therapy but are not necessary for the simple physical therapy procedures that are required in 95 per cent of the trauma cases

Again, physical therapy is in bad repute with many insurance companies and even industrial boards because too many surgeons having no knowledge of true physical therapy have employed light treatment at $2 a treatment for a large number of their cases Take a stiff elbow One can treat it for months and years by the best light treatment ever invented and never secure one whit of functional restoration, whereas early heat, gentle massage and daily, gradually increasing passive and, above all, active exercises will, in the majority of cases, result in full restoration of function

Nor can good results be expected from turning these patients over to an untrained office assistant with instructions to give physical therapy It requires a well trained, intelligent technician and one perfectly willing to use her hands in massage and patient, prolonged muscle training exercises to secure the best results

Finally, physical therapy should not be limited to office practice or to the ambulatory case It should start, in many instances, while the patient is still in the hospital, during the early days of his recovery Therefore, every modern hospital must be equipped with a physical therapy department supervised by a surgeon who understands this work and manned by these trained technicians who can administer it. While visiting hospitals I see many of them equipped with diathermy machines or expensive quartz lights but with no technician capable of going from patient to patient to give massage here, exercise there and heat in nearly every case Simple equipment and intelligent handwork are the acme of successful physical therapy

OCCUPATIONAL THERAPY

To the surgeon engaged in industrial practice who has observed the marked improvement in a disability case after being placed at some light employment in the industry, the idea of occupational therapy should not be new Work is one of the greatest therapy measures and one often neglected It takes the mind off of one's disabled state. It improves morale and awakens or renews interest in creating something and gives promise of future usefulness to one whose future seemed hopeless Thus it can be made diversional or purposeful

C B, a Polish boy, 19 years of age and only a common school graduate, had worked for five years in a printing plant He was a laborer without much future. Then a heavy roll of paper fell from a height, struck him across the shoulders, and "jack-knifed' his spine. As a result, he suffered a severe fracture of the first lumbar vertebra with immediate complete paralysis of his lower extremities Within two hours a laminectomy was performed and the cord freed

There followed a year before he was again able to walk, seven months of which was spent in St Luke's Hospital Physical therapy started the first day by careful protection of the feet from foot drop Within two weeks light massage was started, followed at the end of another week by very mild but definite muscle-training exercises About this time the occupational therapy technician taught him to weave and later to make baskets We talked to him of his future and after a time he became interested in reading and then studying grammar and mathematics He was led to see that his future work must be with his head At the end of six months he was able to go to the work shop in the hospital and there he spent hours trying to run the gig-saw by pedaling Before leaving the hospital he had succeeded After going home he pedaled his mother's sewing machine. He reported every other day to the physical therapy laboratory and here continued his physical rehabilitation. By the end of a year he was able to walk with the aid of two canes He entered a business school and learned shorthand and typewriting He has now been at work for two years as a typist in the same printing plant. He goes to night school and has almost completed a course in accounting He walks everywhere with the aid of only one cane.

This is the story of rehabilitation It involves correct surgery, immediate attention to preservation of function and later physical therapy to restore function Occupational therapy entered into the process, first diversional, then purposeful as an aid to restore function and later as a means of retraining for new work Today this Polish boy says, with a huge grin on his face, "It was a lucky day for me when I broke my back"

CONVALESCENT CARE

It costs from $3 to $4 a day to keep an injured worker in the wards of most hospitals It really costs the hospital from $4 50 to $5 50 a day to maintain these beds

A study of this problem for several years has revealed that in at least 25 per cent of the cases of trauma the patients are kept in the hospital for weeks and months for several reasons, namely, for the convenience of the attending surgeon, because compensation laws include hospital care and the patient prefers to remain as it cuts down expenses at home, because the injury, as a fractured femur, requires months to heal, because too often the patient rooms and boards and there is no one to look after him if he leaves the hospital and because too often home environments contraindicate convalescence Provisions for this period of convalescence is the missing link in the chain of caring for the sick and disabled There is a way station needed between the hospital and back to the job Because of this missing link, industry and the hospitals are both paying an enormous sum annually

Convalescent centers, such as the one maintained by the Burke Foundation and several maintained by hospitals in New York as well as the convalescent homes scattered over the country, can be operated at an average cost of $2 a day for each patient Think of the saving to industry and to the hospital if 25 per cent of the ward patients, after a month or six weeks in the hospital for acute diseases, could be transferred to a convalescent center

In such a center, occupational therapy, physical therapy, outdoor exercise and even vocational training replace the idleness, the reading of cheap novels, the card games and the gossiping and complaining of food and nurses which make up the life of the average ward patient in the average hospital It is difficult to make the hospital for acute diseases the cheerful, hope inspiring, busy place that can be made of the convalescent center The one is to care for the acute cases, the other to rehabilitate the cases of prolonged disability It is applicable to a large percentage of both our medical and surgical cases

It may take years to put across this idea, but it must come as a part of any definite, complete rehabilitation program

PLACEMENT

When the injury is received in any one of several large industries, the replacement in employment of the disabled or handicapped individual is not usually a difficult problem The enlightened industry today as a rule provides jobs for their handicapped employees, disabled in the course of employment

But there are hundreds and thousands of handicapped individuals in every community, because of illness or of injuries received at home or on the streets, for whom employment is one of the gravest problems of our time It is surprising how many of these individuals are refused jobs because they cannot pass the medical examinations of large industries, and smaller industries do not need them

In Chicago, cooperating with the State Free Employment Bureau, the Council of Social Agencies, through its Committee on the Care of the Disabled, has organized a Central Placement Bureau for the Handicapped During the last year this bureau placed more than 500 handicapped men and women at lucrative employment Impressed by the work, a group of business men have just organized an advisory council for the Central Placement Bureau and have pledged themselves to finance the bureau so that its work and usefulness can be extended

This is not medical work, yet if, as surgeons, we are aiming for an economic end-result for our patients, it is one of the most important steps in the rehabilitation program It is a movement which every medical man should abet in every possible way

FOLLOW-UP

In the doctor's office of the large industry, every opportunity is afforded the plant surgeon to follow up his cases In this way he can see that their rehabilitation is completed and so remains

For those of us not so situated we must develop our follow-up clinics or office hours devoted to seeing these patients with permanent disability periodically until assured that full functional restoration, as far as is humanly possible, has been secured, that the work they are doing is compatible with their handicap, and above all that the microbe of dependence has not entered the case and undone all our efforts to rehabilitate At St Luke's Hospital we have found that these follow-up clinics have had the greatest influence toward arousing the interest of the physician in the future welfare of his patient

CONCLUSION

This, then, is the story of rehabilitation of the disabled In many respects it is still an ideal, yet each year, since the end of the World War, has seen some new development that has brought the ideal nearer the goal of practical application More and more physicians are thinking in terms of physiologic medicine, reconstructive medicine and reconstructive surgery Hospitals are adding occupational therapy and physical therapy departments and the staffs are gradually learning to use them for the better improvement of functional results Follow-up clinics are being added State and private organizations are developing vocational training and placement centers for the handicapped

The Council on Physical Therapy of the American Medical Association offers one of the best examples of the growth and development of this ideal into practical application The Council was organized five years ago and was made up of physicians and scientists of the Association The work of weeding out the good from the bad in physical therapy required considerable time Gradually they have come to recognize that physical therapy and occupational therapy are adjuncts to the usual medical and surgical procedures which represent a continued interest in the patient's disability beyond the acute stage, an interest that, properly directed, will assure the greatest possible functional restoration in every disability case This year the Council is thinking less in terms of "machine therapy" and more of those methods which will prevent disabilities and which will give rehabilitation to the disabled

122 South Michigan Avenue

Council on Pharmacy and Chemistry

NEW AND NONOFFICIAL REMEDIES

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for admission to New and Nonofficial Remedies A copy of the rules on which the Council bases its action will be sent on application

W A Puckner Secretary

ALPHANAPHTHOL — Alphanaphthol — 1 hydroxy naphthalene, $C_{10}H_7OH$

Actions and Uses—The actions of alphanaphthol resemble those of betanaphthol The literature is rather contradictory and unsatisfactory as to the relative toxicity, but it is probably of a similar order Alphanaphthol is employed locally as an antiseptic and germicide it is not generally used internally For a discussion of the action and effects of naphthol compounds see Naphthol Compounds, New and Nonofficial Remedies, 1930, p 286

Dosage—Externally, solutions and ointments containing from 0.1 to 1 per cent of alphanaphthol are used, as a gargle vaginal douche and urethral irrigant, solutions containing 0.05 to 0.5 per cent are used

Alphanaphthol occurs as colorless or faint gray glistening crystals or a white crystalline powder possessing a faint phenolic odor and a pungent taste, readily soluble in alcohol ether chloroform and benzene very slightly soluble in hot water and practically insoluble in cold water readily soluble in aqueous solutions of alkali hydroxides A saturated aqueous solution is neutral to litmus. Alphanaphthol melts between 93 and 95 C

A cold saturated aqueous solution of alphanaphthol, when mixed with ammonia water develops a bluish fluorescence Dissolve about 0.1 Gm in 5 cc. of a 20 per cent aqueous solution of potassium hydroxide add 1 cc of chloroform and gently warm the mixture to 50 C the aqueous layer becomes a blue color changing to green and finally brown Dissolve about 0.1 Gm in 5 cc. of sodium hydroxide solution and add 5 cc. of tenth normal iodine solution a violet turbidity results (*distinction from betanaphthol* which gives a clear colorless solution) Place 1 Gm in a 250 cc. Erlenmeyer flask add 50 cc. of water boil for five minutes cool filter through paper and divide into separate portions of 10 cc each to one portion add 1 cc. of a saturated aqueous solution of bleaching powder a dark violet coloration results followed by a flocculent precipitate of the same color changing to reddish brown (*distinction from betanaphthol* which gives a pale yellow color and is bleached by an excess of reagent) To a second portion add 0.5 cc of ferric chloride solution a milky opalescence results gradually turning red and changing to a violet (*distinction from betanaphthol* which gives a pale green color) Shake about 1 Gm. with 50 cc of water in a glass stoppered cylinder at frequent intervals for fifteen minutes and filter separate portions of 10 cc. yield no opalescence with 1 cc. of diluted nitric acid and 1 cc of silver nitrate solution *(halides)* no turbidity with 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution *(sulphates)* no coloration or precipitation on saturation with hydrogen sulphide *(salts of heavy metals)*

Incinerate about 1 Gm of alphanaphthol accurately weighed the residue does not exceed 0.05 per cent. Dissolve about 1 Gm. accurately weighed in 10 cc of a 10 per cent aqueous sodium hydroxide solution collect the insoluble material if any, on a Gooch crucible transfer the insoluble material with 3 portions of a diluted sodium hydroxide solution (1 part of sodium hydroxide plus 99 parts of water) using 5 cc. 5 cc. and 3 cc. respectively finally wash with 2 portions of water using 5 cc. each dry and weigh the alkali soluble material does not exceed 0.1 per cent

ALPHA-NAPHCO—Compound Solution of Alphanaphthol—Alpha naphco contains alphanaphthol 10 Gm, glycerin 32 Gm, soft soap (prepared from cottonseed oil and potassium hydroxide) 23.8 Gm, water to make 100 Gm, gluside and essential oils to flavor

Actions and Uses—See preceding article under alphanaphthol When tested against *B typhosus* by the U S Hygienic Laboratory method, alpha-naphco has a phenol coefficient of 1.46

Dosage—See preceding article under alphanaphthol

Manufactured by the Carel Laboratories, Redondo Calif No U S patent or trademark

PYRIDIUM—Phenylazo-2-6-diamino pyridine monohydrochloride —Phenylazo-α α diamino pyridine monohydrochloride $C_6H_5N\ N\ C_5H_3N\ (NH_2)_2(2)(6)\ HCl$ The monohydrochloride of an azo dye of the pyridine series, phenylazo-α-α diaminopyridine Pyridium contains 28 per cent of nitrogen

Actions and Uses—Pyridium has marked penetrating power and is non toxic and non-irritant in therapeutic dosage It is rapidly eliminated through the urinary tract It is bactericidal in aqueous solution against staphylococcus streptococcus gonococcus, *B coli* and even *B diphtheriae* It is proposed for use in gonorrheal infections urinary diseases, and in colon bacillus and mixed infections In addition to its oral administration it is proposed for irrigation and other local application on the basis of its lack of harmfulness and of its bactericidal activity

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SATURDAY, JULY 5, 1930

FOOD POISONING

The expression "ptomaine poisoning" has been for the most part abandoned in medical discussions and diagnosis during the last few years Ptomaine was the term introduced by Selmi about 1850 and applied to a group of basic substances, having alkaloidal properties, which were obtained from decomposing proteins and were highly toxic to animals, when injected Presently, however, the rapidly developing knowledge of bacteria and their possible role in the genesis of disease directed attention to the microbiotic aspects of the subject

As Damon [1] has pointed out, since the studies were made that directed attention to the possibility that bacteria might be the etiologic agents in causing illness in man in cases that had previously been regarded as ptomaine poisoning, the bacteriologic investigations of many workers have widened our field of knowledge and shown that a variety of bacterial species are capable of growing in foodstuffs under widely different conditions, and that they must be held accountable for many, if not nearly all, cases of food poisoning formerly attributed to ptomaines In fact, Damon notes further, at the present time improved methods of detection are more and more frequently indicating that infection of food is responsible for illness in those who consume it It thus seems probable to Damon that practically all food poisoning, in which illness is not induced by a hypersensitiveness of the individual or by a metallic poison, or in which an alkaloid of vegetable origin is not involved, is due to infection

Thus the bacterial theory of food poisoning has gradually supplanted the older and somewhat less specific ptomaine or chemical theory Perhaps it would be more in accord with actual practice to say that investigators of cases of food poisoning, as the present nomenclature expresses it, seek the presence of pathogenic bacteria or their products in the food under suspicion There are increasing indications that toxic material as well as noxious bacteria need to be taken into consideration Indeed, this may in some ways represent a return to the older chemical theory, with the exception that the materies morbi is directly attributed to the metabolism of well defined and recognized micro-organisms This is exemplified in the recent report of Jordan [2] of the University of Chicago Incriminated food secured during an outbreak of food poisoning contained a yellow staphylococcus in considerable abundance This apparently produced a toxic substance in broth, as shown by the effect of the sterile filtrate, which, on being swallowed by a human volunteer, gave rise to nausea, diarrhea and prostration of the same character as that observed in the original outbreak Furthermore, Jordan has now demonstrated that various strains of staphylococci of diverse origin and different cultural characters are capable of generating in broth a substance which, when taken by mouth, produces gastro-intestinal disturbance This substance is destroyed by boiling and is either destroyed or greatly weakened by being heated at from 60 to 65 C for thirty minutes It seems not unlikely to Jordan that bacteria of other groups may produce similar substances that are irritating to the human alimentary tract From the standpoint of recognizing the immediately harmful factor in many instances of food poisoning, the development of toxic derivatives deserves new emphasis It is fortunate that such toxic substances usually lose their potency when suitably heated

A CRITICAL CONSIDERATION OF OBESITY

Obesity has been described as a state in which the amount of fat stored in the body is excessive The depletion of this fat reserve therefore is the end sought in all attempts at the reduction of obesity Theoretically, at least, this should be accompanied by a reduction in the energy intake to such an extent that the body will be required by the exigencies of the inevitable metabolism to consume some of its energy reserves to meet the current needs The process may be accelerated by increasing the demands for energy This means, first of all, by augmenting the amount of work done Muscular exercise always increases the conversion of energy and is the foremost factor in determining the food requirement on the one hand or the tissue catabolism on the other

These are the seemingly simple principles on which the augmentation, maintenance or depletion of the body energy reserves may be assumed to depend in adult life when growth or the production of new tissue is not under consideration Gain or loss of fat becomes a matter of physiologic bookkeeping, representing the balance between supply and demand in the organism If this were the whole story, the problem of altering body weight should be comparatively simple It usually is Now and then, however, despite a marked reduction in the energy intake, decrease in body weight apparently is not attained Indeed, persons have been known actually to gain in weight on an admittedly inadequate energy intake Such experiences have led to the classification of obesity into exogenous and endogenous types, the latter being ascribed to "constitutional disease that unrelentingly causes a proprogressive deposition of adipose tissue, independent of activity or dietary habit" As might be expected, the omnipotent endocrine glands are assumed to develop the anomaly in which restriction of food intake fails to lead to weight reduction

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[1] Damon S R Food Infections and Food Intoxications Baltimore Williams and Wilkins Company 1928

[2] Jordan E O The Production by Staphylococci of a Substance Causing Food Poisoning J A M A. 94 1648 (May 24) 1930

In considering some of the assumptions of so-called endogenous obesity, Newburgh and Johnston[1] of the University of Michigan Medical School have insisted that obesity is always caused by an overabundant inflow of energy The excess is deposited as adipose tissue They remind us of features that are all too often overlooked in the study of human size that body weight is the resultant of two factors—gain or loss of tissue and a gain or loss of water The loss of one and a gain in the other may neutralize each other, or a large retention of water may cause a gain in weight, even though body tissue has been consumed, and may lead an observer who fails to take water exchange into account to draw erroneous conclusions

The studies at Michigan in which the water balance as well as the energy debit and credit are taken into account leave no doubt that the response of various types of obese people does not differ from that of normal people All of them oxidize body tissues in accord with the prediction from the caloric deficit Retention of water may proceed for several days or loss of water may be suddenly precipitated The body weight from day to day under conditions of reduction in energy intake may show no parallelism to the expected figures In the long run, however, the body weight almost always approaches the predictable figure In reply to the query as to how long a person may maintain his weight in the face of a diet deficient in calories, Newburgh and Johnston cite their own observations that the failure to lose weight is only a matter of days Thus far the longest period observed by them has been sixteen days, usually it is shorter

Much of the mystery in the attempts at reduction of obesity is thus dispelled The principle of the conservation of energy remains intact when the facts of the behavior of the obese are presented in quantitative fashion The disproportions leading to obesity may be classified, according to the Michigan clinicians, into two categories The first group includes various human weaknesses, such as overindulgence and ignorance The second group is composed of conditions that cause a decrease in the requirement for energy, such as lessened activity or lowering of the basal metabolic rate for any reason If the long established food habits do not respond to this lessened demand, obesity is inevitable The fundamental feature of obesity remains a positive energy balance On that basis it can be intelligently treated

METABOLISM DURING PROLONGED REST

For many years, physiologists were content to adopt the doctrine of the school of Voit and his followers with respect to the effect of muscular exercise on nitrogenous metabolism This tended 'to displace protein from the position of primacy to which it had been raised by Liebig" Until recently the dominant current view suggested that muscular work does not increase protein metabolism, furthermore, the character of the protein metabolism has been regarded as essentially unchanged by ordinary muscular activity This is not intended to deny that under unusual conditions, when fat or carbohydrate are not readily available, protein may become the main source of energy in the body

Cathcart[1] of Glasgow has challenged the older contentions As he presents his claims

> Let it be granted then that the main supply of energy is drawn from non nitrogenous sources, still the substance of the muscle is rich in nitrogen. It would be ridiculous to argue as if muscle were a stable mechanical arrangement like a practically unwearable jeweled bearing The fact that if the conditions are not optimal, there is very soon unmistakable evidence of excessive wear and tear is definite proof of the delicate chemical balance which exists in muscle. The question must then necessarily be raised, Is there no evidence of an increased output of nitrogen as the result of muscle activity?

To this query Cathcart has made a positive reply After reviewing the abundant experimental evidence he has reached the conclusion that there is abundant evidence in support of the view that muscle work leads to a definite though perhaps limited increase in the output of nitrogen, i e to increased catabolism of protein, and at the same time there is also good evidence that the same muscle activity leads to the laying down of protein, i e, to the stimulation of the anabolic processes in the broadest sense of the term In other words, the existent evidence points to a definitely enhanced metabolism of protein as the result of muscle activity

Clinicians are often interested in the results of the reverse process, namely, enforced muscular inactivity or rest The wastage or atrophy of muscles in disuse is a familiar picture Disuse may be of varied sorts voluntary rest, immobilization to correct deformities or promote healing of parts, or that due to destructive lesions of the lower motor neurons or their axons, or to toxic action, or to pressure Cuthbertson[2] of the University of Glasgow has lately reported carefully conducted balance experiments on persons brought into nitrogen equilibrium in a preliminary fore period and then subjected to enforced inactivity of the lower limbs Muscular rest of the order described causes an almost immediate but small rise in the output of urinary nitrogen As the period of rest lengthens, it appears probable that the rate of increase is accelerated but that eventually it declines to a more steady level, depending on the degree of immobilization Surveying the results obtained in work experiments with those just referred to, Cuthbertson concludes that when one alters the level of functional activity there is a lag period before nitrogen equilibrium is again obtained During this period there is a loss of the essentially active substance, which persists until, in the case of increased muscle work, the anabolic response is equal and opposite to the increased catabolism, or even greater In the case of decreased activity, it persists until the amount of functioning metabolic substance is reduced to such a level that the catabolism is equal and opposite to the diminished anabolism Such a change does not appear to alter appreciably the endogenous metabolism as represented by uric acid and creatinine The gaseous metabolism remains constant from day to day Thus our knowledge of nonuse of the muscles and bones may match the current information on the effects of their use A physiology of rest is desirable quite as well as a physiology of exercise

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[1] Newburgh L. H and Johnston Margaret W Endogenous Obesity—A Misconception J Am. Dietet. A. 5 275 (March) 1930

[1] Cathcart E. P The Influence of Muscle Work on Protein Metabolism Physiol Rev 5 225 (April) 1925

[2] Cuthbertson D P The Influence of Prolonged Muscular Rest on Metabolism Biochem. J 23 1328 1929

RICKETS AND VITAMIN D

At present the pathogenesis of rickets seems to be fairly well defined, few of the advances in the science of nutrition have been made with as striking an outcome as has been the case with this disease The relationship of the inorganic constituents of the diet, the specific effect of cod liver oil, the curative effect of natural and artificial ultraviolet rays, and the activation of ergosterol to antirachitic potency are mile posts along the road of progress in elucidating the etiology and biochemical relationships of rickets The novelty of producing a therapeutic agent by photochemical means together with the tremendous potency of viosterol has led, perhaps, to an undue canonization of this material on the part of physicians Without detracting in the least from its merited value in the treatment of rickets, certain recent observations raise a question as to the simplicity of the pathogenesis of rickets implied in the current facile use of viosterol

Recently it has been pointed out[1] that, whereas both viosterol and cod liver oil are extremely efficacious in curing rickets, only the latter contains in addition the indispensable vitamin A Although the most obvious function of calcium and phosphorus is in the building of bones, there are other demands for these mineral elements which, at times such as pregnancy and lactation, become of great importance Brown and Shohl[2] have indicated clearly that, whereas vitamin D is concerned with the calcification of bones, the retention of calcium and phosphorus in the body is largely a function of the level of these materials in the diet, irrespective of the presence or absence of vitamin D Indeed, these conclusions are fortified by the apparent futility of attempts to influence the utilization of calcium during lactation in various species by measures known to accelerate the healing of rickets

If there exists a complacent belief among some investigators that rickets is due to a deficiency of vitamin D alone, there are others who do not accept such a simple relationship In a recent study, De Sanctis and Craig[3] have compared the efficacy of cod liver oil and of viosterol as prophylactic antirachitic agents, using comparatively large groups of infants as subjects Employing materials of proved potency and in liberal amounts they found that of 123 children given viosterol 29 per cent were not protected against rickets, while of 100 given cod liver oil 3 per cent showed rickets, although the former group received twice the number of units of vitamin D given the latter group The children were all similar in age, in duration of time on the experiment, in dietary treatment and in rate of growth Rather than to accept the obvious conclusion that the recommended dosage of viosterol is too small to prevent rickets, the authors are inclined to believe that the results indicate that other circumstances in addition to lack of vitamin D are responsible for the development of rickets

On the basis of recent experiments on laboratory animals, Hess and his co-workers[4] have concluded that the level of inorganic phosphate in the blood is not as infallible a criterion of rickets as heretofore believed By carefully adjusting the various components of the experimental ration together with vitamin D in the form of viosterol or cod liver oil, they have been able to increase the concentration of serum phosphate without at the same time inducing healing of the rachitic lesion Likewise rickets was cured without raising the level of blood phosphate to the normal value The fact that in these studies the cure of rickets was independent of the concentration of inorganic phosphate in the blood indicates that variation of this constituent "cannot be regarded as an essential or inherent feature in the pathogenesis of healing of this disorder" Furthermore, these investigators conclude that local disturbances in the epiphyses of the bone as well as chemical disturbances in the systemic blood play a part in the causation of rickets

Modern medicine has been helped enormously by the sciences, and in no field has biochemistry rendered greater service than in connection with the deficiency diseases The newer knowledge of the pathogenesis of rickets attests this fact However, the innermost workings of the cell are yet to be plumbed, chemistry and physics have explained much in both experimental and practical medicine, but the *tactus eruditus* is still a jewel of great worth

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[1] Vitamin D in Tuberculosis editorial J A M A 94 414 (Feb 8) 1930

[2] Brown Helen B and Shohl A T Rickets in Rats J Biol Chem 86 245 (March) 1930

[3] De Sanctis, A G and Craig J D Comparative Value of Viosterol and Cod Liver Oil as Prophylactic Antirachitic Agents J A M A 94 1285 (April 26) 1930

[4] Hess, A F Weinstock Mildred Rivkin Helen and Gross J J Biol. Chem. 87: 37 (May) 1930

Current Comment

THE PRESIDENT-ELECT—E STARR JUDD

The newly elected President of the American Medical Association, Dr E Starr Judd of Rochester, Minn, is widely known to the medical profession of America as a calm, sincere, practical and competent surgeon He was born in Rochester, July 11, 1878 After preliminary general education he received his degree in medicine from the University of Minnesota School of Medicine in 1902 He served his internship in Saint Mary's Hospital in Rochester and thereafter became first assistant to Dr Charles H Mayo Since that time he has progressed steadily in the work of the Mayo Clinic, heading one of the sections in the division of surgery He has aided education in surgery, serving as professor in the Graduate School of the University of Minnesota Dr Judd has been constantly active in organizational work in county and state medical societies and has been president of the Minnesota State Medical Association During the war he was a major in the Medical Officers' Reserve Corps and on active duty as director of a school of instruction in anesthesia and surgery, reaching finally the rank of lieutenant colonel In many scientific medical organizations devoted particularly to surgery, including the Western Surgical Association, the American Surgical Association, the Society of Clinical Surgery and the American College of Surgeons, he has been a constant attendant and participant in the programs From the time of his entrance into surgical practice, Dr Judd has contributed extensively to the periodical literature of his subject, especially abdominal surgery His fundamental investigations are recognized for their merit both in this country and abroad His contributions have won for him the recognition of his colleagues as a competent leader in this field By his election, the House of Delegates of the American Medical Association recognizes the importance of surgical science and establishes again its conviction of the necessity for realizing that the American Medical Association is above all a body of men devoted to the prevention of disease, its care and its treatment

E Starr Judd, M D
President Elect of the American Medical Association

THE DETROIT SESSION

The multitude of provisions for instruction and entertainment at the Detroit session was perhaps the most striking feature of the annual session of the Association just held in that city Some activity was scheduled for satisfactory use of every moment of the visitor's time, and it remained only for him to employ his time to his own best advantage. From the first two days, during which a series of extraordinary clinical lectures and talking motion pictures were available, to the last three days, in which the fifteen scientific sections provided more than three hundred manuscripts on various phases of medical progress, scientific discourse occupied the auditorium and the halls in the Masonic Temple At the same time, the greatest number of scientific and technical exhibits ever assembled under the auspices of the Association held forth in every available space on several floors in the same building For the evening the Michigan State Medical Society provided a past-presidents' dinner for the opening night, given exclusively for the officers and the House of Delegates, the opening meeting with the presentation of emblems to past-presidents took place on Tuesday night, numerous fraternity and other social entertainments were held on Wednesday, the President's reception on Thursday, and boat rides, motor bus trips and private tours were provided by the Local Committee on Arrangements for the intervening periods, if any Obviously, complete utilization of such provisions placed a tax on the physical endurance of the convention guest, and a course of rest and physical training in anticipation of the session was almost necessary to enable the too enthusiastic conventionist to survive successfully the session's attractions The meetings of the House of Delegates were marked primarily by the demonstration of confidence in the work of the Board of Trustees and by special interest in the economic problems affecting the progress of medicine today Thus, resolutions concerning the care of veterans' legislation federal aid on maternal welfare, mental hygiene and similar problems dominated the picture It is significant that the resolution concerning aid for veterans adopted by the House of Delegates was specifically referred to by the President of the United States in his message vetoing the veterans' bill The attendance of more than five thousand physicians in a time of financial stress indicates the manner in which the medical profession accepts the importance of this annual session The appreciation of all of those who attended must be tendered to the Local Committee on Arrangements, which contributed freely of its funds, its time and its efforts to build the success of the meeting The hospitality shown has established the profession of Detroit in the affections of the Fellows of the American Medical Association

PERFUMES AND PIGMENTATION

The use of cosmetics and perfumes has grown to enormous proportions in recent years The fad is no longer confined exclusively to women The male of the human species has begun to exhibit occasional indulgence in cutaneous applications that were once frowned on as unmasculine The physician is only secondarily concerned with the social proprieties, the personal peculiarities or the possible implications of these growing customs Lotions and perfumery play a part in present-day life among a sufficient number of persons to raise the question of the physiologic wisdom of the practice Dermatologists may not agree as to the desirability of the repeated applications of alcoholic solutions, such as most lotions are, to the skin, they may differ with respect to the use of various types of greases more elegantly designated as cosmetics or skin creams All admit, however, that idiosyncrasies occur which express themselves in various types of dermatitis A remarkable pigmentation of the skin, originally described by Freund[1] in 1916 and later named berlock dermatitis by Rosenthal,[2] has been subjected to renewed observation in this country by Gross and Robinson[3] at Columbia University College of Physicians and Surgeons The condition results from the application of toilet waters to the skin immediately before it is exposed to the sunlight Eau de cologne and also oil of bergamot, which is one of the essential oils used in toilet waters, have been found to have photosensitizing properties The dermatitis that can be induced by artificial ultraviolet irradiation as well as by sunlight after applications of perfumes to the skin is usually found on the neck and chest and appears as dark red areas changing to brown slightly mottled with red The shape of such an area is usually similar to that of an area covered by a small drop of flowing fluid, and it generally appears during the summer The New York dermatologists raise the question whether one is dealing with a personal susceptibility or with several factors, such as climate, perspiration, brand of perfume and short intervals between application of inciting cause and exposures to sunlight In view of the fact that perfumes and toilet waters are so widely used and that sunbaths have become so popular, they are inclined to think that there must be some predisposing factor The number of cases seen and the number of people under the conditions seeming to cause this dermatitis are not in proportion In any event, the lovers of sunshine and the patrons of alpine rays may do well to bear in mind that in some persons the daub of the perfume bottle stopper may bring about leopard spots where they were not expected

TRICHINOSIS IN CALIFORNIA

The Journal[1] has previously directed attention to the decidedly increased morbidity of trichinosis in California The number of cases reported at that time was 84 Cases, however, continue to be reported until they now number 151 with 9 deaths That some epidemiologic factor is active appears to be definitely proved since the yearly number of cases reported in 1928 and 1929 were 29 and 33, respectively In fact, the *Bulletin of the California State Department of Public Health*, April 19, makes this significant statement 'The past five months have brought to California a larger number of cases of trichiniasis than have ever occurred within the state during a like period of time" The consumption of salami accounted for 45 cases alone out of 132 cases reported It is interesting to note that smoked bear meat caused 4 cases As would be expected, many persons were made ill from home-killed and home-prepared pork products Commercial products however, were far from being exempt since cases were attributed to the consumption of these in Alameda Sacramento and San Francisco counties The situation, apparently, demands that every effort be exerted by health officials to ascertain the source of the infected food, to use all known safeguards of preparation of pork and its products, and to disseminate widely the knowledge that thorough cooking in the home will kill the parasite Moreover, microscopic examination of hogs and rats in various centralized areas should be pushed in an endeavor to discover possible endemic foci

Association News

MEDICAL BROADCAST FOR THE WEEK

American Medical Association Health Talks

The American Medical Association broadcasts at 10 o clock, daylight saving time on Monday, Tuesday, Thursday and Saturday over Station WBBM (770 kilocycles or 389 4 meters)

The program for the week of July 7 12 is as follows

July 7	The Problem of the Epileptic
July 8	Reducing is All the Rage
July 10	Measuring Human Energy
July 12	My Son Goes to Kindergarten

Five Minute Talks may be heard over the Columbia Broadcasting System daily from 1 to 1 05, daylight saving time

The program for the week is as follows

July 7	How to Develop a Healthy Mind
July 8	Living Outdoors
July 9	A Daily Chart for the Runabout.
July 10	Sick Headaches
July 11	Gaining the Child s Confidence.
July 12	What is Pellagra?

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[1] Freund Dermat Wchnschr 63 931 1916

[2] Rosenthal F Zentralbl f Haut u Geschlechtskr 13 322 1924

[3] Gross P and Robinson L. B Berlock Dermatitis Arch. Dermat & Syph 21 637 (April) 1930

[1] *An Outbreak of Trichinosis Current Comment* J A. M A 94 562 (Feb 22) 1930

PROCEEDINGS OF THE DETROIT SESSION

MINUTES OF THE EIGHTY-FIRST ANNUAL SESSION OF THE AMERICAN MEDICAL ASSOCIATION, HELD AT DETROIT, MICHIGAN, JUNE 23 27, 1930

(Continued from page 2074)

Second Meeting—Tuesday Morning, June 24

The House of Delegates was called to order at 9 30 a m by the Speaker, Dr F C Warnshuis

The Speaker announced that, if there was no objection, the signed attendance slips of the individual delegates would constitute the roll call of the House

It was moved by Dr J N Vander Veer, New York, seconded by Dr Sol G Kahn, Utah and carried, that the House dispense with the reading of the minutes

Supplementary Report of the Reference Committee on Credentials

Dr J D Brook, chairman, reported that 148 delegates had filed satisfactory credentials On motions duly seconded and carried, Drs Burt R Shurly, Section on Laryngology, Otology and Rhinology, J Q Graves, Louisiana, W F Draper, U S Public Health Service, Charles B Wright, Minnesota, James T Case, Section on Radiology, and E S Edgerton, Kansas, who had been properly certified as delegates but had lost their credentials, were seated

Report of Reference Committee on Rules and Order of Business

Dr David Ross, chairman, presented the following report

On the resolution offered by Dr E C Thrash, Georgia, the committee recommends that it be not adopted as the intent of the resolution is already covered by a rule of the House of Delegates

Respectfully submitted

David Ross, Indiana, Chairman
W H Seemann
B L Bryant
E. A Hines

On motion of Dr Ross seconded by Dr J W Burns, Texas, the report was adopted, after discussion by Dr Southgate Leigh, Virginia

Dr Mather Pfeiffenberger, Illinois, suggested that the Secretary read each one of the reports

Report of the Reference Committee on Medical Education

Dr Irvin Abell, chairman, presented the following report

Your committee recommends for adoption that part of the resolution presented June 23 by Dr E P Sloan Illinois, reading as follows

Resolved That this House of Delegates of the American Medical Association do herewith approve and commend the good work being done by the Council on Medical Education and Hospitals and be it further

Resolved That the Council on Medical Education and Hospitals of the American Medical Association be urged to continue this important work, and increase its activities along this line until the American Medical Association is generally recognized as the proper organization in this country to standardize hospitals

Your committee has reviewed with care the report of the Council on Medical Education and Hospitals and has noted with interest the contained resume of the activities of the Council during the twenty-five years of its existence It is especially pleasing to note that the Council had opportunity during its twenty-fifth year to grant class A rating to a school of medicine which will open Oct 1, 1930 with school building and hospital equipment accommodating 300 medical students and 200 patients provided after an expenditure of four million dollars Record is made also of a medical library of 20,000 volumes and approximately 300 medical journals installed and subscribed for by this particularly fortunate educational institution We mention this recent experience of the Council on account of the marked contrast to its earlier experiences in assisting the struggles of other institutions in order that they might achieve class A rating

We recommend to this House of Delegates and the constituent associations represented recognition of the extent and the complexity of the work of the Council in their control over medical schools, hospitals, clinical and radiologic laboratories We note the Council s reference to its lack of legal authority over any institution but would emphasize the fact that its moral authority may not be denied since this council represents 90 per cent of the active practitioners of medicine in the United States

We were especially interested in the reference to the preceptorial assignments by various medical schools of their senior students and believe that a report of the reactions of students, preceptors and medical schools to this practice would be of interest to the next House of Delegates

We believe also that the material accumulating in the files of the Council relative to so called advertising of hospitals will be of future interest

We submit that the work done by the Council on Medical Education and Hospitals since its creation in 1904 has been remarkably constructive and is in large measure responsible for the high standards, ideals and character which today are dominant in American medicine and further that its accomplishments in the past may be taken as an index of its further attainments in the investigations now under way

Respectfully submitted

Irvin Abell, Chairman
Walter F Donaldson
Holman Taylor
Isaac A Abt

On motions of Dr Abell, duly seconded and carried the report was adopted section by section and as a whole, after discussion by Dr Donald Macrae, Jr, Iowa, and Dr Olin West, Secretary

Report of Reference Committee on Sections and Section Work

Dr H A Royster, chairman, presented the following report

The Committee on Sections and Section Work begs leave to submit the following report

1 We endorse the arrangements of sections as outlined in the report of the Council on Scientific Assembly

2 We approve the action of the Council on Scientific Assembly in substituting clinical lectures for diagnostic clinics and in changing the hours

Respectfully submitted

H A Royster, Chairman
J F Smith
J R Bloss
Southgate Leigh

Dr Royster moved that the report be adopted The motion was seconded by Dr David Ross, Indiana, and carried

Report of Reference Committee on Hygiene and Public Health

Dr W F Draper chairman, presented the following report

The Committee on Hygiene and Public Health reports favorably on the resolution presented by Dr J D Brook, Michigan, designed to reduce the hazard from small attachments to children's toys which may become detached and then aspirated into the lungs, and recommends the adoption of this resolution

Respectfully submitted

W F Draper, Chairman
C W Waggoner.
C E. Humiston
W R Steiner
Albert Soiland

On motion of Dr Draper, seconded by Dr Mather Pfeiffenberger, Illinois, the report was adopted

Report of Reference Committee on Reports of Board of Trustees and Secretary

Dr Grant C Madill, chairman, presented the following report

THE SECRETARY'S REPORT

We endorse the sentiment expressed in the report of our secretary in which he recommends a more active and aggressive program on the part of component medical societies, stressing the necessity for unified action on the part of the medical profession as being essential in maintaining leadership in all questions pertaining to health matters Also the importance of establishing and maintaining the hearty cooperation of both the state and the county organizations through the agency of their respective public relation committees

We recognize the changing method in medical practice, however we earnestly urge a realization of the necessity of maintaining the personal relationship between physician and patient, and oppose any attempt on the part of any well meaning but misinformed and misguided individuals or organizations in their efforts to apply 'mass production' methods to the practice of medicine

We approve that portion of the report advocating the education of the public in all matters pertaining to health and disease

We concur with the idea expressed that the medical profession has been too reticent and conservative in taking a position of active leadership in health activities, particularly with reference to the education of the public along these lines

We believe that it would be a decided aid to organized medicine if the members of the House of Delegates would avail themselves of the opportunity of attending the annual conference of the state secretaries

We congratulate the Association on the manner in which its affairs have been conducted the past year by its able and efficient manager and secretary Olin West

REPORT OF BOARD OF TRUSTEES

We heartily commend the Board of Trustees for the financial showing made as exemplified by the auditor's report for the past year A review of the report emphasizes the wisdom of the action of the house in authorizing the increase in the subscription price of The Journal to meet the demands of the increased Association activities

We are gratified by the position of The Journal as the leader of medical publications, as well as the special journals in their respective fields

We believe that Hygeia has a place in every physician's waiting room and the attention of Fellows should be called to this fact

We emphasize the value of the library and commend its more general use.

We endorse the work of the various councils for the past year as detailed in this report

We especially commend the work of the Bureau of Legal Medicine and Legislation with reference to national legislation in connection with the narcotic bill and the Sheppard-Towner Maternity and Infancy Act.

We approve of that part of the report with reference to the World War Veterans Act wherein attention is called to the viciousness of this proposed legislation and we recommend that this House of Delegates go on record as being opposed to the federal government giving all medical and surgical care to veterans suffering from injury or disease that is not service connected.

We recommend the methods employed by the Bureau of Legal Medicine and Legislation and urge close cooperation of the various state legislative committees with this bureau

We approve of the educational campaign that has been inaugurated by the Bureau of Health and Public Instruction and recommend a continuation of the cooperative policy with the National Educational Association and National Congress of Parents and Teachers

The value and importance of the Annual Scientific Exhibit cannot be overestimated and we recommend that it be continued and expanded from year to year

The Trustees' report as a whole reflects decided progress in the Association's affairs Your committee desires to express its realization of the immense amount of work entailed and its appreciation of their worth-while labors in connection therewith

Respectfully submitted

Grant C. Madill, Chairman.
R W Fouts.
Ephraim R Mulford
J Norman Henry
J W Van Derslice

On motion of Dr Madill, duly seconded and carried, the report was adopted section by section and as a whole, after discussion by Drs Donald Macrae, Jr Iowa, C P Kindleberger, United States Navy, and Dr Holman Taylor, Texas

Dr Donald Macrae Jr, Iowa, moved that a letter signed by the Secretary and the Speaker be sent to the American Legion headquarters in Indianapolis and also to the American Legion auxiliary headquarters, presenting the matters discussed. The motion was seconded by Dr A A Ross, Texas and adopted, after discussion by Drs Olin West, Secretary, G Henry Mundt, Illinois H H Shoulders, Tennessee, D E Sullivan New Hampshire, B F Bailey, Nebraska, Donald Macrae, Jr, Iowa, and Walter F Donaldson, Pennsylvania

Address of Dr Hubert Work

The Speaker introduced Dr Hubert Work, first Speaker of the House of Delegates, who said

Mr Speaker, Members of the House of Delegates and Fellow Members of the American Medical Association, including Past Presidents

I assure you it is a great pleasure, after an absence of ten years, to stand before you and look you in the face. I have no message to bring you I am pleased to see you, pleased to hear this discussion, pleased to note the enthusiasm, and I am sure that the House of Delegates has been left in more able hands than it was in when I occupied this Chair

Temporary Reader

Dr Mather Pfeiffenberger, Illinois, moved that the Speaker appoint a temporary reader for this session to read the reports The motion was seconded by Dr T O Freeman, Illinois, and carried

The Speaker appointed Dr G Henry Mundt, Illinois, temporary reader

Report of Reference Committee on Amendments to the Constitution and By-Laws

Dr E. C Thrash, chairman, presented the following report

The Judicial Council recommends that our By-Laws be changed in reference to the induction of fellows into the American Medical Association, which will require that Chapter XI, section 2, have the following paragraph added

> Any member of this association holding a degree equal in requirement to that of M D granted by a school of medicine recognized by the American Medical Association entitling the holder to apply to a state board of medical examination and registration for license to practice medicine and who on the prescribed form shall apply for fellowship and subscribe for The Journal, paying the annual fellowship dues for the current year shall be inducted into the Association as a Fellow unless the application is disapproved by the Judicial Council.

Pursuant to the resolution introduced by Dr Harris of California recommending that a new council be made to function for the American Medical Association which shall be called "Council on Medical Economics" and which resolution carries a recommendation for a change in the By-Laws, we recommend that, should the House of Delegates adopt this resolution, the By-Laws be revised as follows

Amend chapter VII, Committees, section 3 by adding after "(*c*) Council on Scientific Assembly" '(*d*) Council on Medical Economics"

Amend chapter VIII, Organization of Standing Committees or Councils, section 1, by adding the words "The Council on Medical Economics shall consist of ——— members each elected for ——— years" after the sentence "The Council on Medical Education and Hospitals shall consist of seven members each elected for seven years"

Amend chapter VIII, Sec. 2, Officers, by adding after 'The Board of Trustees shall elect annually to serve one year a secretary of the Council on Medical Education and Hospitals" the words and a secretary of the Council on Medical Economics and shall fix their salaries"

Amend chapter IX Duties of Standing Committees or Councils, by the addition of a section 4 to read 'Section 4 Council on Medical Economics The functions of the Council on Medical Economics shall be (1) To investigate conditions of medical economics and to suggest means and methods by which the same may be improved (2) To endeavor to further the realization of such suggestions as may be approved by the House of Delegates '

That portion of the report dealing with the amendment to chapter XI, section 2, in reference to the induction of fellows into the American Medical Association was held over for the next meeting of the House

The remainder of the report, dealing with amendments to chapter VII, section 3, chapter VIII sections 1 and 2 and chapter IX, by the addition of section 4, providing for a Council on Medical Economics, was referred back to the committee until the House should receive the report of the Reference Committee on Reports of Officers after discussion by Drs Wendell Phillips, Past President, Henry C Macatee, District of Columbia, and E C Thrash, Georgia

Report of the Board of Trustees

Dr Edward B Heckel, chairman, presented the following report

SUPPLEMENTARY REPORT OF BOARD

1 *Saving of Tax on Earned Income*—At the Portland session the Board of Trustees reported that it had authorized the employment of counsel to represent the interests of the medical profession in the adjustment of complaints that had been received against the method used by some collectors of internal revenue in computing the earned incomes of physicians who employ professional assistants The matter had come to an issue in the Arnett-Crockett Clinic at Lafayette Ind At the request of Drs Arnett and Crockett, counsel for the American Medical Association cooperated with counsel employed by them The matter has been settled in a manner that should be entirely acceptable to the medical profession

It had been held that professional fees, to constitute earned income, must be received as compensation for personal services rendered by the individual taxpayer On the basis of that ruling physicians rendering personal services, but employing professional assistants had in some instances been denied the right to include as earned income all their professional fees up to the statutory limit of $30,000 It was held that the payments received for services to patients who came in part under the personal observation of the principal physician and in part under the personal observation of one or more of his assistants did not in their entirety constitute income earned by the principal The earned income of the principal in any such case, it was held was the difference between the amount received by him from the patient and the amount paid by him to his assistant for the assistant s services in treating the patient

As the result of the Arnett Crockett case the Commissioner of Internal Revenue has issued instructions for the guidance of the collectors of internal revenue as follows

> It was not intended to deny the taxpayer the right to consider the entire amount received as professional fees as earned income if the taxpayer is engaged in a professional occupation such as a doctor or a lawyer even though the taxpayer employs assistants who perform part or all of the services provided the client or patient is that of the taxpayer and looks to the taxpayer as the responsible person in connection with the services performed
>
> This ruling will also apply to income received as professional fees from a professional partnership even though the partnership employs assistants who work on a salary basis provided the clients or patients are that of some active member of the partnership and look to some active member of the partnership as responsible for the services performed

The cooperation of the American Medical Association in this case rendered it possible to procure not merely a decision in the particular case submitted on appeal to the Commissioner of Internal Revenue but also a ruling by the commissioner broad enough to cover physicians generally and the promulgation of that ruling in such a way as to avoid similar difficulties arising in the future and to facilitate the procuring of refunds by physicians who through the mistaken interpretation of the law have been called on to pay income taxes in excess of the amount due In the Arnett-Crockett case the taxpayers will receive, by virtue of this ruling, refunds for two years, with interest amounting to approximately $700 and they in common with all other taxpayers similarly situated will save considerable amounts every year in the future, because of the corrected method of computation It is obvious that the money saved to the medical profession—and incidentally to all other professions in which professional assistants are employed—will be considerable

2 *Changes in Tariff of Interest to Physicians*—Under the recently enacted tariff bill, duties have been increased on a considerable number of articles necessary for the diagnosis and treatment of disease constantly used by physicians and hospitals Against the overwhelming tendency for increases in duties it was almost impossible to make any headway, but on the item of the greatest interest to the medical profession surgical instruments the increase was held down to a point far below that demanded by American manufacturers of surgical instruments All of the duties stated below are ad valorem duties Under the tariff act of 1922 the duty on surgical instruments was 45 per cent American manufacturers of surgical instruments urged that the new bill impose a duty of 75 per cent plus varying specific duties based on the cost of each article The act just signed by the President rejects all proposed specific duties and provides that the duty on surgical instruments, including hypodermic needles hypodermic syringes and forceps composed wholly of metal, shall be 55 per cent unless in chief value of glass, in which case the rate shall be 70 per cent The tariff on pharmaceutic and surgical articles and utensils of all kinds used in hospitals laboratories and colleges and universities, wholly or in chief value of glass except bottles, vials etc, is increased from 65 per cent to 85 per cent The tariff on optical glass or glass used in the manufacture of lenses or prisms for spectacles or for optical instruments or equipment is increased from 45 per cent to 50 per cent On hemocytometers, ophthalmoscopes corneal microscopes testing or recording instruments for ophthalmologic purposes and frames and mountings the tariff is increased from 45 per cent to 60 per cent. The tariff on electrotherapeutic and x-ray apparatus and instruments is increased from 30 per cent to 35 per cent It will be regretted if the increased duty paid by importers at ports of entry will be made the excuse for increases in retail prices far greater than the increase in the duty and will in the end be reflected in the cost of medical, surgical and hospital care

3 *The Work of the Committee on Foods*—The work of the Committee on Foods a special committee of the Council on Pharmacy and Chemistry has developed in a remarkable manner The response of manufacturers of food products in submitting these products for the consideration of the committee has been greater by far than was anticipated and many of those who have submitted products have been quick to acquiesce in the findings and rulings of the committee This work has developed so fast and to such an extent that it has become necessary to employ an executive officer to administer the affairs of this committee The members of the Committee on Foods are E M Bailey New Haven Conn , Eugene F DuBois New York Julius H Hess, Chicago, W McKim Marriott, St Louis, L B Mendel, New Haven,

Composition: Cartilage is the predominant tissue and may be of hyaline, fibrous or elastic type. The lobules of cartilage are separated by a loose, sometimes myxomatous, connective tissue which is associated with clefts and cystic spaces lined by cuboidal or columnar cells. Smooth muscle fibers are frequently seen and fat is almost invariably present, both at the periphery and occasionally in the center of the tumor. Hamartomas are also sometimes classified as mixed tumors and almost all cartilage-containing tumors of the lung are hamartomas. Two pure chondromas of the lung have been reported.

Complications: Zeithofer[4] reported a hamartoma with carcinomatous change, invasion of bronchial wall and metastasis to hilar lymph nodes. This is of rare occurrence, and may represent concomitant carcinoma of bronchial epithelium not at all associated with the primary hamartoma. Several cases have been described of carcinoma in the same or opposite lung as the hamartoma. When carcinoma of the lung is associated with hamartoma of the lung, the hamartoma may be erroneously interpreted in the roentgenogram as a metastatic growth of the carcinoma.

Bronchoscopic Appearance: According to Sherrick,[8] endobronchial hamartomas have a smooth, yellow or gray-yellow external surface and are often polypoid or pedunculated.

Roentgen Characteristics: Most hamartomas are unattended by symptoms and are discovered in routine x-ray films of the chest, appearing as a

TABLE I
GROSS CHARACTERISTICS OF NINE HAMARTOMAS OF THE LUNG

Number	Age	Sex	X-Ray Film Visualization	Site*	Location	Diameter In Cm.	Associated Pulmonary Disease	Color and Consistency
1	76	F	No	RLL	Parenchymal	2.6	Lobar pneumonia	Yellow-white, firm
2	76	F	No	LL**	Subpleural	....	Bronchopneumonia, metastatic carcinoma	Pink-gray, firm
3	76	M	No	LLL	Subpleural	1.5	Organizing bronchopneumonia	Yellow, soft
4	56	F	No	RLL	Subpleural	4	Pulmonary infarcts, bronchiectasis	Yellow, firm
5	93	M	No	LUL	Subpleural	3	Bronchopneumonia, bronchiectasis, chronic pneumonitis	White, firm
6	85	F	No	LLL	Subpleural	2	Atelectasis, fibrosis	White, firm
7	68	F	Yes	RUL	Subpleural	3	Purulent bronchitis, bronchopneumonia	Gray-white, firm
8	52	M	Yes	LLL+	Subpleural	1		White, firm
9	59	F	Yes	LUL+	Subpleural	1.5		Gray, firm rubbery

*RLL indicates right lower lobe; LLL, left lower lobe; etc.
**Location in lung was not recorded.
+Tumor was surgically resected.

dense shadow. According to Hall,[15] the appearance of small calcifications scattered through a discrete smooth-margined, round or lobulated mass which is surrounded by normal lung tissue is unusual and should at once suggest a hamartoma. Generally, however, the roentgen features are not diagnostic.

Clinical Features in Present Series

In the past 24 years at this hospital, seven hamartomas of the lung have been encountered in 10,107 autopsies, an incidence of 0.069 per cent. Two other hamartomas were surgically excised during the latter part of the same period. The details of the clinical findings and of the gross features are summarized in Table I. Blocks of tissue from the tumor and in some instances the entire tumor were fixed in 10 per cent formalin, embedded in paraffin, sectioned and routinely stained with hematoxylin and eosin, Masson's trichrome stain for connective tissue, van Gieson's stain, Verhoeff's elastica stain and periodic acid-Schiff stain. In one instance (Case IV) only the microscopic sections, stained with hematoxylin and eosin, were available for study. Details of the histologic structure of these tumors are summarized in Table II.

Sex Distribution: In the 20 hamartomas reported by McDonald and his associates[1] the ratio of men to women was 3 to 1, but in our 9 cases the ratio of men to women was 1 to 2.

Age: Although pulmonary hamartomas are found at all ages, most are discovered in older persons at autopsy. In our series the oldest person was 93 years old, the youngest 52 years. In three of our nine patients the tumor was seen on roentgen films of the chest, and in all three cases the lesion was thought to be either a Ghon tubercle or a malignant tumor. In six, failure to visualize the tumors in the roentgen film may be attributed either to its small size or to its obscurement by other pathologic alterations in the lung or pleura.

TABLE II
HISTOLOGIC CHARACTERISTICS OF HAMARTOMAS OF THE LUNG

Histologic Feature	Case Number								
	1	2	3	4	5	6	7	8	9
Cartilage	+	—	—	+	+	+	+	+	+
Hyaline	+	—	—	+	—	+	+	+	—
Elastic	—	—	—	—	+	—	—	—	+
Mesenchymal condensation	+	—	+	+	—	+	+	+	+
Connective tissue	+	+	+	+	+	+	+	+	+
Fat	—	+	+	—	—	+	+	+	+
Smooth muscle	—	—	+	—	—	+	+	+	+
Epithelial cells	+	+	+	+	—	+	+	+	+
Columnar	+	+	+	+	—	+	+	—	—
Cuboidal	+	+	+	+	+	+	+	+	+
Lymphocytic infiltration	+	+	+	+	+	+	+	+	+

+ indicates presence; —, absence.

Gross Pathologic Features

Six hamartomas were located in the right lung and three in the left; five were in the lower lobes, two in the upper, and in one instance (Case 2) the location was not recorded. Eight were found immediately beneath the pleura and one lay deep within the lung parenchyma near the hilum. The maximum diameter ranged from 1 to 4 cm. and the median diameter was 2.6 cm. All the tumors were well circumscribed, most were gray-white, and in two the central portion of the tumor was calcified.

Histopathology

Seven of the tumors contained cartilage; in five the cartilage was hyaline and in two, elastic. The cartilage was bordered by loose, cellular, myxomatous connective tissue which in all cases was PAS-positive. The periphery of the larger nodules frequently contained small satellite nodules of newly formed cartilage as well as condensed areas of myxomatous connective tissue, representing an early stage in cartilage formation. The cartilage was of normal appearance. In one case the hamartoma was composed entirely of elastic cartilage and no epithelial cleft, connective tissue, smooth muscle or fat was observed; this structure was suggestive of the so-called "pure" chondroma of the lung (Fig. 1).

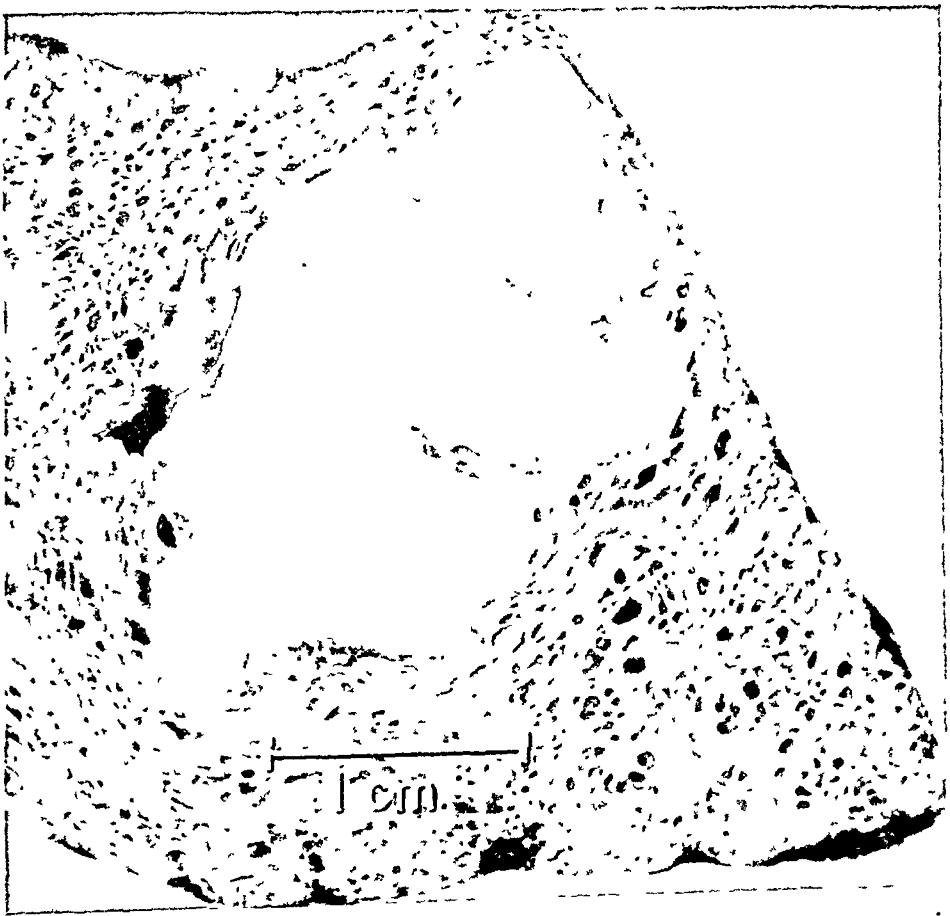

FIGURE 1: Chondroma of lung. The tumor is subpleural and appears to arise in the wall of a bronchus. The surrounding lung is the site of bronchiectasis, severe chronic pneumonitis and fibrosis. (X 2).

Fat: Six of the nine hamartomas contained adipose tissue, usually at the periphery but occasionally in and around small epithelial clefts that extended into the center of the tumor. The adipose tissue was present in the form of small clumps of fat cells but at times individual fat cells were seen in the loose myxomatous connective tissue. In all cases the fat cells were of the adult type.

Connective Tissue: Connective tissue was present in eight tumors and usually was loose and fibrillar. At the periphery dense collagenous fibers frequently formed a pseudo-capsule.

Smooth muscle was found in five instances, appearing as small bundles, and was located in the connective tissues supporting the epithelial clefts.

Epithelial Elements: Small clefts and epithelial-lined cystic spaces were seen in eight cases. Small glands were present beneath the epithelium in several cases; this could represent either true gland formation, or more likely small fragments of epithelium pinched off by the expanding cartilage and connective tissue. The clefts were lined for the most part by cuboidal cells. In several areas, however, there were mucus-secreting, ciliated columnar cells which occasionally showed pseudo-stratification. Most of the epithelium-lined spaces were located at the periphery of the tumor and frequently displayed a polypoid appearance. Occasionally small clefts extended into the center of the tumor, usually along with ingrowths of connective tissue passing between the islands of cartilage (Fig. 2).

Inflammatory cell infiltration was seen in some degree in all cases, usu-

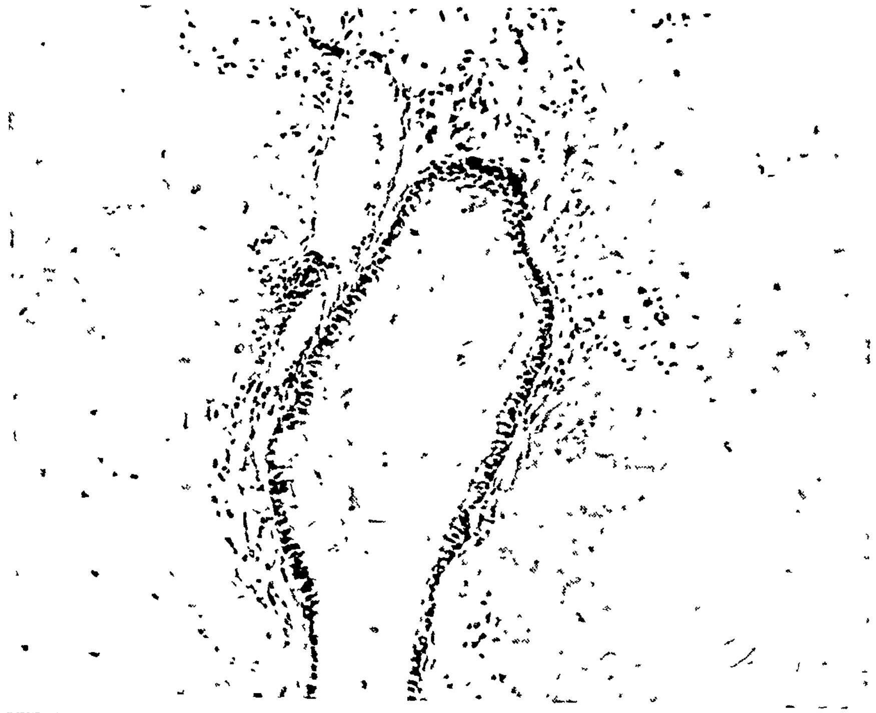

FIGURE 2: Small epithelial cleft of bronchial epithelium enclosed within expanding cartilage. (X 140).

ally mainly at the periphery, in the submucosal connective tissue and in the adjacent lung parenchyma. Most of the cells were lymphocytes, although plasma cells, eosinophils and, more rarely, neutrophilic granulocytes were also present (Fig. 3).

Calcification: In two instances the hyaline cartilage contained focal areas of calcification.

Discussion

The hamartoma usually originated in the wall of the small bronchi or bronchioles in the periphery of the lung and gradually expanded and compressed the adjacent lung parenchyma (Fig. 4). Their appearance suggested growth both into the bronchial lumen as well as into the adjacent lung. In two cases in which the tumors cast x-ray shadows, x-ray films six years previously were negative. In both of them the tumor was later removed because it showed evidence of growth.

Etiology: Four possible mechanisms of origin of hamartomas have been proposed: 1) congenital malformation, 2) hyperplasia of normal structures, 3) neoplasia, and 4) response to inflammation. Most writers feel that these tumors represent a misplaced bronchial anlage. The lungs develop by a process of budding from the primitive bronchi, the most primitive areas being at the periphery. The columnar epitheluim of these primary bronchi is surrounded by membrana propria. The connective tissue framework of the lung gives rise to smooth muscle and cartilage. According to Möller (cited by Carlsen and Kiaer),[7] the tumor is caused by localized abnormality in development of the bronchi; instead of the normal fetal inversion of the terminal tubes of the bronchial tree there may be at one site, inversion of epithelium and mesenchyma. Other writers[6] feel that

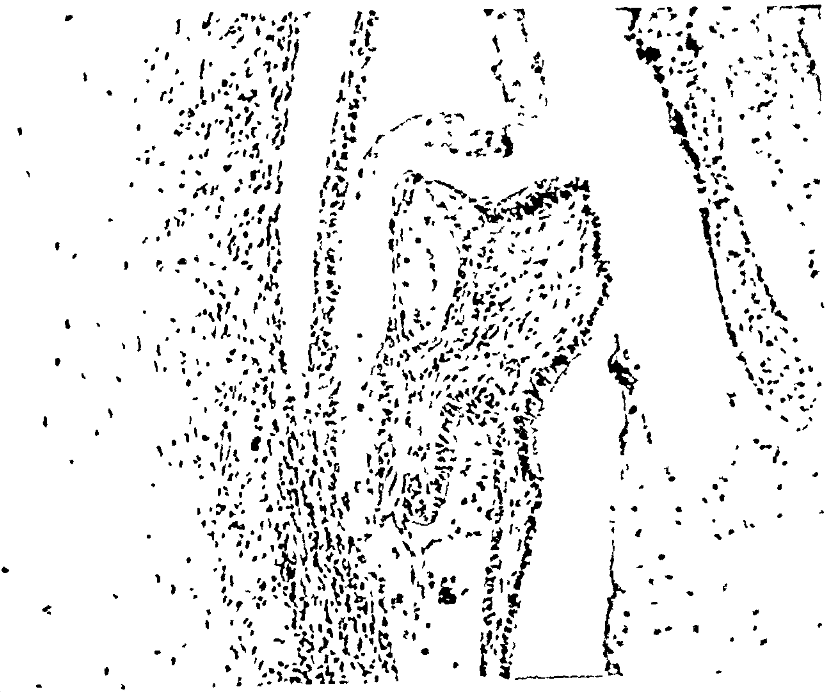

FIGURE 3: Portion of periphery of tumor compressing bronchial epithelium. Note lymphocytic infiltration of subepithelial connective tissue. (X 140).

the tumor arises by proliferation of bronchial epithelium which in its growth mimics development of the bronchi but is directed toward the lumen rather than toward the lung parenchyma. There is no preformed cartilage in the peripheral portion of the lung where most of these tumors arise and it has been adequately demonstrated that in true endobronchial hamartomas, the cartilage of the tumor has no connection with the normal occurring cartilage located in the bronchial wall.[8] Therefore, it appears that the tissues found in the hamartomas arise from connective tissue of the bronchial wall as in fetal development.

In all seven hamartomas found at autopsy, infiltration of lymphocytes, plasma cells and granulocytes were present at the periphery of the tumor and often in the connective tissue which separated the lobules of cartilage. There was also inflammatory reaction in the adjacent pulmonary parenchyma. In most of the lungs chronic inflammation varied from small focal areas of fibrosis associated with lymphocytic infiltration to marked, diffuse, chronic pneumonitis with fibrosis. During resolution of a pneumonic exudate the lung contains an unusually high concentration of fibrinolytic enzyme.[13] The resolution of fibrinous inflammatory exudate and the formation of granulation tissue, according to Selye,[14] is under hormonal control. Since animal experiments indicate that cortisone and corticotropin can prevent fibroplasia, we examined the adrenal glands for evidence of hyperplasia and found that in all cases the adrenal gland showed increase

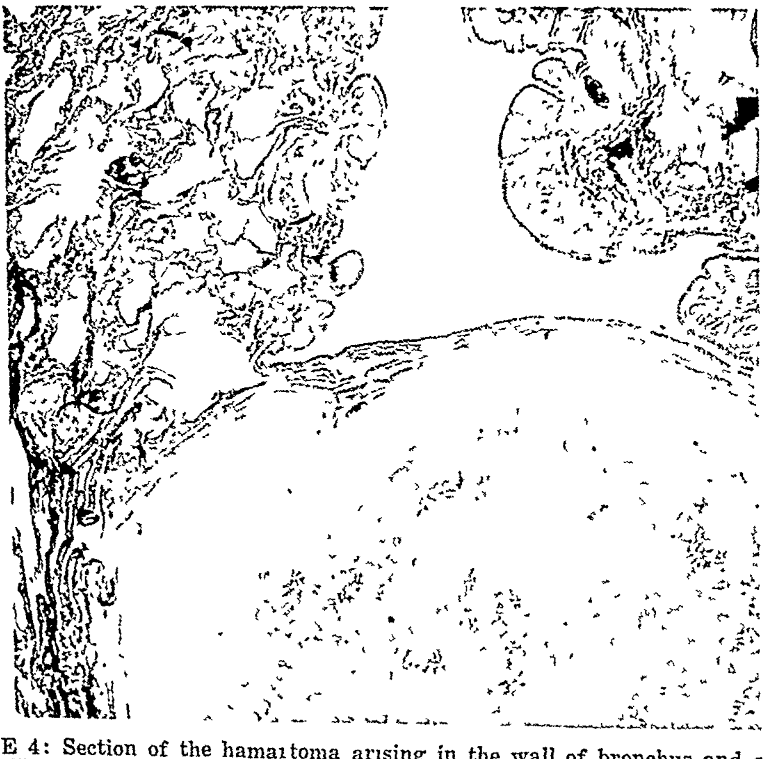

FIGURE 4: Section of the hamartoma arising in the wall of bronchus and extending into its dilated lumen. (X 10).

in the weight of the organ, or increase in thickness of the cortex. Although its significance is not clear, the question may be raised if, in some cases of chronic inflammation of the lung, hyperplasia of the adrenal cortex may not have been responsible for retardation of fibroplasia of the lung.

SUMMARY

Approximately 200 hamartomas of the lung have been reported; 33 of these were of the endobronchial type.

The tumors seldom give rise to symptoms and are usually discovered during routine roentgen examination of the chest. They frequently simulate chronic granuloma or malignant neoplasm on the roentgen film although they rarely if ever become malignant.

Nine new cases are presented, one of which seems to be a "pure" chondroma. The tumors arose from the connective tissue of the bronchial wall and expanded outward into the lung parenchyma as well as inward into the bronchial lumen. All of the hamartomas were associated with an infiltration of chronic inflammatory cells and many were found adjacent to areas of chronic pneumonitis and fibrosis.

The possibility is suggested that chronic inflammation may be a factor, in some cases, in formation of pulmonary hamartoma.

RESUMEN

Se han reportado aproximadamente 200 hamartomas del pulmón; 33 de ellos eran del tipo endobronquial.

Los tumores rara vez dan lugar a síntomas y se descubren habitualmente durante exámenes radiológicos de rutina. Frecuentemente simulan el granuloma crónico o la neoplasia maligna en la radiografía aunque rara vez si acaso se hacen malignos.

Se presentan nueve casos nuevos uno de los cuales parece ser un condroma "puro." Los tejidos nacen del tejído conectivo de la pared bronquial y se expanden hacia afuera dentro del pulmón así como hacia la luz del bronquio. Todos los hamartomas estaban asociados con una infiltración de celdillas inflamatorias crónicas y muchos fueron encontrados adyacentes a áreas de neumonitis crónica y fibrosis.

Se sugiere la posibilidad de que la inflamación crónica sea un factor en algunos casos para la formación del hamartoma pulmonar.

RESUME

Environ 200 cas d'hamartomes pulmonaires ont été rapportés. 33 de ces cas appartenaient au type endobronchique.

Les tumeurs se traduisent rarement par des signes cliniques et sont généralement découvertes à la suite d'un examen radiologique systématique du thorax. Elles simulent fréquemment des granulomes chroniques ou des néoplasies sur le film radiologique, bien qu'elles deviennent rarement malignes, si même elles le deviennent jamais.

L'auteur présente neuf cas nouveaux dont l'un semble être un chondrome "pur." Les tumeurs partent du tissu conjonctif de la paroi bronchique et s'étendent vers l'extérieur, dans le parenchyme pulmonaire, aussi bien que vers l'intérieur, dans la lumière bronchique. Tous ces cas d'hamartomes

étaient associés à une infiltration de cellules inflammatoires chroniques, et beaucoup furent trouvés au voisinage de zones de pneumonie chronique et de fibrose.

L'auteur suggère que l'inflammation chronique puisse constituer dans quelques cas une cause possible de l'hamartome pulmonaire.

ZUSAMMENFASSUNG

Es liegen Berichte vor über annähernd 200 Hamartome der Lunge; 33 von diesen waren vom endobronchialen Typ.

Die Tumoren geben selten Anlass zu Symptomen und werden gewöhnlich im Verlauf von routinemässigen Thorax-Röntgenuntersuchungen festgestellt. Die täuschen häufig auf den Röntgenbild chronische Granulome oder bösartige Tumoren vor, obwohl sie selten, wenn überhaupt, bösartig werden.

Es werden 9 neue Fälle vorgestellt, von denen einer ein "reines" Chondrom zu sein scheint. Die Tumoren entstanden vom Bindegewebe der Bronchialwand und dehnten sich nach aussen in das Lungenparenchym aus, ebenso wie einwärts in das Bronchiallumen. Alle diese Hamartome waren begleitet von einer Infiltration mit chronischen entzündlichen Zellen, und viele fanden sich angrenzend an Gebiete von chronischer Pneumonitis und Fibrose.

Es wird die Möglichkeit vermutet, dass die chronische Entzündung—in manchen Fällen—ein Faktor sein kann beim Zustandekommen von pulmonalen Hamartomen.

REFERENCES

1 McDonald, J. R., Harrington, S. W. and Clagett, O. I.: "Hamartoma (Often Called Chondroma of the Lung)," *J. Thoracic Surg.*, 14:128, 1945.

2 Novi, I.: "Chondromatous Hamartoma and Pure Chondroma of Lung," *Arch. ital. chir.*, 79:315, 1955.

3 Filippi, P.: "Histomorphologic and Histogenetic Study of Primary Bronchopulmonary Chondromata," *Riv. anat. pat. e onc.*, 7:125, 1953.

4 Zeithofer, J.: "Chondroma (Hamartoma) of the Lung," *Beitr. path. Anat.*, 114:271, 1954.

5 Hochberg, L. A. and Pernikoff, M.: "Primary Chondromas of the Lung," *Dis. Chest*, 17:307, 1950.

6 Sutherland, T. W., Aylwin, J. A. and Brewin, E. G.: "Endobronchial Chondromatous Hamartoma. A Report of Two Cases," *J. Path. and Bact.*, 65:93, 1953.

7 Carlsen, C. J. and Kiaer, W.: "Chondromatous Hamartoma of the Lung," *Thorax*, 5:283, 1950.

8 Sherrick, J. C.: "Endobronchial Hamartoma," *Quart. Bull. Northwestern Univ. Med. School*, 26-27:171, 1952-53.

9 Davidson, L. R. and Stern, S. H.: "Hamartoma Simulating Ipsilateral Metastasis in a Case of Primary Bronchogenic Carcinoma," *Dis. Chest*, 26:210, 1954.

10 Thomas, M. R.: "A Cystic Hamartoma of the Lung of a Newborn Infant," *J. Path. and Bact.*, 61:599, 1949.

11 Hood, R. T., Good, C. A., Clagett, O. T. and McDonald, J. R.: "Solitary Circumscribed Lesions of the Lung," *J.A.M.A.*, 152:1185, 1953.

12 Thomas, C. P.: "Benign Tumors of the Lung," *Lancet*, 1:1, 1954.

13 Pokorny, C. and Hellwig, C. A.: "Diffuse Interstitial Fibrosis of the Lungs," *A.M.A. Arch. Path.*, 59:382, 1955.

14 Selye, H.: "General Adaptation Syndrome and Diseases of Adaptation," *J. Clin. Endocrinol.*, 6:117, 1946.

15 Hall, W. C.: "Roentgenologic Significance of Hamartoma of the Lung," *Am. J. Roentgenol.*, 60:605, 1948.

SECTION ON CARDIOVASCULAR DISEASES

Heart Disease of Pulmonary Origin

GEORGE R. HERRMANN, M.D., F.C.C.P. and ALLEN H. SHIELDS, M.D.
Galveston, Texas

It behooves clinical investigators in a University Hospital group to survey from time to time, recorded clinical material on pressing diagnostic and therapeutic problems. Heart disease of pulmonary origin is a pertinent and pressing topic for, when fully developed, it has been considered hopeless by too many physicians. We have, therefore, reviewed our cases in an attempt to reemphasize precipitating and perpetuating conditions, determine predisposing factors and evaluate early diagnostic signs. We hope to touch upon possible prophylactic measures and argue for the establishment of as effective a program of management as possible. We first studied the records of 208 cases, who had been cross filed under the diagnosis of chronic cor pulmonale. It soon became apparent that minimal criteria for the diagnosis of chronic cor pulmonale had to be established, and after considerable study we arrived at those set down in Table I. We were acutely aware that chronic cor pulmonale is an end result of an insidious process. Furthermore we were fully conscious of the difficulty of arbitrarily drawing a line separating definite cor pulmonale from pulmonary disease with positional electrocardiographic changes.

The application of our criteria, as outlined here, has limited our study to patients with definite respiratory disease and pulmonary hypertension, and definite right atrial and right ventricular enlargement; as shown by the electrocardiogram or the teleradiogram. In addition, we have accepted the presence of right heart failure, without left failure, as presumptive evidence of right ventricular enlargement, even when other signs were equivocal. Patients with tricuspid or pulmonary valvular

TABLE I
CRITERIA FOR DIAGNOSIS OF PURE COR PULMONALE

1. Evidence of Hypertension of the Pulmonary Circuit
    - A. Midsternal or Epigastric Heave
    - B. Pulmonary Diastolic Shock
    - C. Sharply Accentuated & Split P_2
2. Definite Evidence of Right Ventricular Enlargement
    - A. ECG-Right Axis Deviation, P_2 & P_3 Tall and Sharp; High R in V_1
    - B. Radiogram
    - C. Right Heart Failure without Left Heart Failure
3. Absence of Significant Valvular Lesions, Systemic Hypertensive or Ischemic Heart Disease with Myocardial Infarction
4. Symptoms and Signs of Pulmonary Disease

Cardiovascular Service, University of Texas Medical Branch.

TABLE II
ANALYSIS OF 208 CASES DIAGNOSED AS COR PULMONALE

1. Definite Pure Cor Pulmonale	51
2. Lung Disease with Some ECG Changes, But No Demonstrable Hypertrophy or Failure of the Right Ventricle	32
3. Cases with Complications: Systemic Hypertension, Infarctions, Left Failure, etc.	60
4. Cases of Pulmonary Disease in Which Cardiac Changes were Minimal or Absent	44
5. Cases in Which the Primary Pathology was Extra Pulmonary	21
TOTAL	208

disease, constrictive pericarditis, systemic hypertension, ischemic myo*cardial changes and congestive failure of the left ventricle and a few* rare or equivocal conditions were specifically excluded. Patients with mitral stenosis and congenital cardiac lesions were intentionally omitted, even though they were known to have increased resistance to pulmonary flow, and pulmonary hypertension. The vascular changes were secondary to heart disease and no primary lung disease was present.

Pulmonary function studies have added much to our concepts of the physiology of the cardio-respiratory system.[1, 2] However, these are mainly of value in the early detection quantitating, localizing and differentiating the pathology in the lung. Respiratory tests have been utilized only to a limited extent in studying secondary cardiac changes and were neglected in most of our cases, even though they promise much in early diagnosis.

In Table II, we have grouped the findings of our 208 cases, with which *we began our study. By our criteria, there were among these 208 records* only 51 indisputable pure chronic cor pulmonale cases. An additional 32 had pulmonary disease, many with various electrocardiographic findings, but in these we could not demonstrate right heart enlargement or failure. Another 60 cases were excluded at the beginning because of complicating cardiovascular diseases. In 44 the cardiac changes were insignificant and in 21 there was no evidence to substantiate pulmonary origin of the clinical picture.

In Table III, we have listed some of the unusual conditions which have

TABLE III
UNUSUAL CONDITIONS SIMULATING CHRONIC COR PULMONALE

1. Carcinoma of Lung impinging on Pulmonary Artery
2. Intracardiac Aneurysm
3. Thrombosis of Pulmonary Artery
4. Essential Pulmonary Hypertension
5. Constrictive Pericarditis
6. Tricuspid Valvular Disease

TABLE IV
AGE, SEX AND RACE OF 51 PATIENTS WITH COR PULMONALE

Age	No. of Cases	Per Cent of Total	Sex and Race	
0 - 10 years	2	4	White Male	31
10 - 20 years	2	4		
20 - 30 years	1	2	Colored Male	10
30 - 40 years	4	8		
40 - 50 years	10	20	White Female	6
50 - 60 years	15	30		
60 - 70 years	14	28	Colored Female	4
70 - 80 years	3	6		

been confused with cor pulmonale in this series. The exclusion of some of these cases may seem arbitrary, as for example, bronchogenic carcinoma impinging on the main pulmonary artery is clearly lung disease with secondary right heart failure. However, we felt it desirable to exclude those conditions without significant impairment of pulmonary function.

We have analyzed our cases in regard to age, and these data are shown in Table IV. Though there was a rather widespread distribution, the high incidence in the middle aged groups has been demonstrated. This is probably due to several factors. Lung disease must be present for a considerable time to produce changes, and the development of atheromatous degeneration will decrease cardiac reserve and serve to precipitate right heart decompensation. Two status asthmaticus deaths in two of our young patients were of great interest, these children seen in the first decade of life had mucovicidosis, with recurrent bouts of respiratory infection and with chronic bronchial infections. Both died before the age of two and incidentally, both had relative anemias instead of the polycythemias, usually present in pulmonary hypoxia.

The sex and race incidences of patients with cor pulmonale shown in Table IV indicate an overwhelming preponderance of white males in our group which is also a finding worthy of some attention. There must

TABLE V
ETIOLOGY OF 51 CASES OF PURE CHRONIC COR PULMONALE

Asthma-Bronchitis-Emphysema	33
Bronchiectasis	6
Congenital Cyst of Lung	3
Pulmonary Fibrosis	2
Pneumoconiosis	2
Coeliac Disease	2
Other Conditions	3

be more than one factor responsible for this, and we have considered a greater exposure of men to industrial dusts and colds. The higher incidence of untreated asthmatic bronchitis and of atheromatous changes in males were judged significant. The probably more frequent use of tobacco by men might appeal to some as contributing to this disproportion. We have no explanation for the racial difference except that the non-caucasions in this area, are of lower socio-economic status and might have succumbed to other causes before the full-blown cardio-pulmonary syndrome had time to develop.

In Table V, the asthma-emphysema syndrome is shown to be the principal etiology. These individuals invariably had had chronic plastic bronchitis and episodes of status asthmaticus were common. Two of them had complicating kyphoscoliosis and emphysema. The cases of congenital cysts of the lung are of interest for while they are relatively rare, they may be amenable to radical therapy, and two of the three patients have been subjected to surgical resection, with improvement. The cases of pneumoconiosis have been rare in our area but are important to note, in that they may probably be avoidable, and have been prevented by proper industrial hygiene.[3]

The Electrocardiogram in Cor Pulmonale

In analyzing in detail the electrocardiograms of these patients, we found, as was to be expected, that sinus tachycardia was extremely common, and in fact, was the predominant rhythm. It was interesting to find that the incidence of atrial fibrillation was only 6 per cent, which is rather rare in contrast to its frequency in conditions characterized by left atrial dilatation. This may be related to the lack of myocarditis in our patients. We found, in those with dilated conus arteriosus, the typical electrocardiographic picture of right axis deviation, electrically vertical position and clockwise rotation of the heart. Peaked P waves in II, III and AVF, were more frequently seen in younger patients who were not likely to have complicating myocardial disease. Evidence of right ventricular

TABLE VI

		Hematocrit	Plasma Volume	RBC Mass	Total Blood Volume
Cor Pulmonale 17 Cases	Average	56.4	+ 8.5	+48.1	+27.2
	Maximum	66.0	+37.0	+83.0	+46.0
	Minimum	*48.0*	—23.02	*+21.0*	0.0
Uncomplicated Emphysema 6 Cases	Average	43.5	+ 3.3	+ 4.3	+ 5.8
	Maximum	45.0	+12.0	+19.0	+19.0
	Minimum	40.5	— 9.0	— 8.0	— 9.0

(where possible, the values found before digitalization were used) hypertrophy, in precordial leads was not commonly seen. The tracing of V3R, and V4R would probably have added to our evidence but these leads were not recorded routinely on most of our patients.[4] We analyzed various R:S ratios in the different leads, as well as many other possibly significant points but were unable to discover any further additions to the previous diagnostic features. Vector cardiography promises some help in the early recognition of slight right ventricular hypertrophy.

Heart Failure and Blood Mass Alterations

In 80 per cent of our 51 cases of cor pulmonale congestive heart failure was present and all of these were subsequently digitalized. It is notable that 13 (25.5 per cent) of these patients developed abnormal rhythm or other signs of digitalis intoxication sometime during our observation. This complication was probably due to efforts to push too far the cardiac

TABLE VII
BLOOD VOLUME STUDIES, PLASMA, RBC MASS AND TOTAL IN PATIENTS WITH COR PULMONALE IN FAILURE AND IN COMPENSATED STATES IN PERCENTAGES ABOVE AND BELOW NORMAL VALUES

Patient	Age	Weight Kg.	V.P. Cm. Saline	Hb. Gm. Per Cent	Hct.	P.V. I_{131}	RBC Mass Cr_{51}	Total B.V. P.V. and RBC M.
E. L. P.	42	53	18 10	20.1 19.0	66 64	+11 —11	+83 +48	+44 +21
J. D. C.	54	87	21 11	19.2 21.5	61.8 63.3	+ 2 —29	+33 +42	+17 + 4
O. R.	57	53	22.5 15	18.0 15.4	58 40	+32 — 5	+95 +47	+61 +18
R. B.	25	60	27	16.8	58.5	—18	+46	+11
C. K.	48	66	20	16.3	58.5	+37	+57	+46
C. O. D.	68	76	24	17.0	56	+16	+28	+21
W. H.	61	90	25	17.0	55	—20	+54	+14
J. A.	49	62	30+ 31	16.5 15.4	54.8 55.2	+34 +11	+63 +14	+41 +12
B. E.	59	50	12	15.6	55	— 5	+23	+20
W. E. T.	67	64	7	17.0	49	—23	+26	± 0
L. L.	42	61	28 12	14.2 14.8	48 50	+27 — 1	+21 +14	+24 +11
E. H.	55	39	10	15.3	45	+ 3	+ 7	+19
D. D.	52	80	12	16.8	45	+ 5	+19	+11
J. C.	43	56	11	15.0	45	+ 3	+10	+ 6
A. A.	68	45	12	14.6	42	+12	+ 5	+ 9
C. W.	63	77	10	12.9	40.5	— 9	— 8	— 9
J. W. S.	35	79	11	14.5	43.5	+ 7	— 7	+ 1

glycoside to control this rather refractory form of failure.

Digitalis and diuresis of 5 of the cor pulmonale patients with failure resulted in decrease of plasma volume to below normal values. Oddly enough, the erythrocyte mass also decreased markedly in three of these cases by an average of 44 per cent while two showed no significant change. There has been subclinical jaundice demonstrated in some of these instances as evidence of a hemolytic component, but it did not seem to be of the magnitude to explain these differences. The possibility of shift of the red blood cell mass and erythrocyte sequestration were considered.

The severe cases almost invariably had polycythemia, but when we tabulated our data, the hemoglobin values ranged from 22 gms. per cent to 10.0 gms. per cent with an average of 16.1 gms. per cent which is just above the upper limits of normal for our laboratory. Nearly 40 per cent of the 51 patients had a normal value but 5, or 9.8 per cent had a complicating anemia. The results are summarized in Table VI and show the hematocrit varied from 66 per cent to 48 per cent with an average of 56.4 per cent. The venous pressure was, of course, increased in those patients with right ventricular failure. It has been noted by Reilly and by Lewis et al that the total blood volume is expanded in most cases of heart failure[6, 7] four of which had cor pulmonale.

Detailed blood volume studies on 17 of our patients were done using Cr_{51} to study the red blood cell mass by the methods of Sterling and Grey[8] and plasma volume studies were done with I_{131} by the method of Crispell et al.[9] We studied six cases with uncomplicated emphysema for comparison. The results are shown in Table VI as change in per cent above and below our normal for an individual of a similar age, sex, and body surface area. These are shown in detail in Table VII. Although there was some variation of plasma volume and only three showed a significant increase of 30 per cent or more, the red blood cell mass was consistently elevated with value ranging from +21 per cent to +83 per cent with an average increase of +48.1 per cent.

The total blood volumes were derived by addition of plasma volume and red blood cell mass and ranged from no increase to an increase of 46 per cent in the cor pulmonale patients with an average increase of 27 per cent. In contrast only four of the six emphysema patients showed increases with values ranging from —8.1 per cent to +19.0 per cent and an average of +9.0 per cent. These findings were not considered outside of the normal range.

Bronchopulmonary Measures

In the management of these patients, we would first emphasize prophylaxis, that is, control of pulmonary disease to delay or prevent cardiac changes. We have learned to practice vigorous treatments of asthmatics and desensitization to allergin if such are demonstrable.

First and foremost in management are measures aimed at alleviation of bronchopulmonary condition and any contributing focus as sinusitis or tonsillitis. We would again emphasize the value of antibacterial agents for the prompt control of bronchial infection in a primary or recurrent flare-up. Bronchodilators, as anti spasmodics, aminophyllin, wetting agents and mucous digestants have been used frequently in recent years in our hospital. The most common plan has been a combination of aerosols as Isuprel, aerolone and Alevaire, in equal parts, either by a No. 40 De Vilbiss nebulizer, or with intermittent positive pressure oxygen apparatus of the Monaghan type. Aminophyllin (0.25-0.5 gm.) intravenously is often life saving. Abdominal pads and binders or pneumoperitoneum to elevate the diaphragm, with the hope of increasing the bellows action and augmenting the vital capacity may sometimes help. Most of our patients receive instruction in diaphragmatic breathing exercises, to increase the efficiency of the abdominal bellows.[10] All of these measures seem to add to longevity and postpone complications.

Industrial safeguards which are being more and more applied should be advocated as they will, in time, tend to reduce the incidence of pneumoconiosis and subsequent fibrosis. We have found potassium iodide in a saturated solution, carefully administered in gradually increased dosage to produce rather marked symptomatic relief in a large number of patients, particularly those with an allergic bronchitis component. Adrenal cortical steroids are apparently of some value in those allergic patients with eosinophilia, and prednisone or prednisilone would be preferable to cortisone or hydracortisone because of the decreased tendency to salt and fluid retention and potassium excretion.

Cardiovascular Procedure

Management of cardiac complications has largely been directed toward an attempt to correct myocardial failure. Venesection with blood letting until the hemoglobin is 13 gm. and the hematocrit is below 50, is usually beneficial. Digitalis, when indicated by clinical signs of failure with increased venous pressure is of value, and its efficacy may tend to vary directly with the extent to which ischemic myocardial changes complicate the picture. Mercurial diuretics are of value in reducing the hypervolemia of heart failure. Diamox has been most commonly used in these patients, because of the well known complication of respiratory acidosis and elevated CO_2.[11] We have used 250 to 500 mgs. of diamox every day or every other day, adjusting the dosage to the individual requirements. Reduction of the blood volume in acute episodes with phlebotomy has rarely been necessary, and should be done carefully. In hypervolemic polycythemic patients 500 cc. is usually sufficient to bring the hemoglobin to 12-13 gm. and the hematocrit to 45 to 50 gm.

In addition to these rather specific measures, we have advocated reduction of activity to *reduce oxygen requirements* of the tissues and a sedative as phenobarbital in moderate doses by mouth which seemingly has been of aid. Recently, the use of radio Iodine I_{131} in euthyroid patients has been advocated, in an effort to reduce metabolic needs by intentionally inducing a hypothyroid state. It would seem preferable to use drugs of a temporary antithyroid type, as propyl-thiouracil or tapezol. These agents have been used to a limited extent, and the therapy seems to be of some definite value. We have felt that the relatively heroic iodine destruction of thyroid tissue should be reserved for the most severe cases, at least until further studies make optimal dosage a more predictable quantity.

Finally, we must briefly mention the psychotherapeutic aspect of this disease, which, in common with other chronic, progressive conditions, continues to be a significant feature from the patient's point of view at any rate. An aggressive, confident, or optimistic attitude by the doctor must be an integral part of the successful management of these unfortunate victims.

The adoption of a nihilistic attitude by the physician, can contribute as much to a patient's decline as any other factor.

Discussion

In these studies we have been impressed with the frequency of the insidiously developing pulmonary disease in patients in the wake of recurrent bronchitis. Patients are asymptomatic between attacks for 20 to 30 years because of the great 20 fold reserve of the lungs during the first phase of the disease.[12] The subsequent development of chronic hypertensive coronary artery heart disease or chronic valvular disease, may obscure the signs of predominant right heart enlargement. Under these circumstances, the pulmonary condition is often subclinical and overlooked until an acute respiratory infection precipitates symptoms.

It is certainly advantageous to the patient to have had a potential or a subclinical diagnosis prophetically made in the first phase by a wise and cautious physician, before symptoms of pulmonary origin develop, for then long postponement may be accomplished. Every recurrent or chronic cough, every asthmatic attack especially with increasing residual air in the lung, gradual decrease of exercise tolerance and fatigability, should suggest developing emphysema in the middle aged man.

The respiratory dead space increasing more rapidly than normal with aging, causes the second phase of symptoms to progress more rapidly over a period of five to eight years. The chest expansion and movement of the lung borders decrease, the timed vital capacity drops off as the residual air volume increases and the anteroposterior diameter increases slowly, almost imperceptibly. The electrocardiographic signs of right axis deviation, S1 increasing, PII and especially Vi sharpening and R developing in V1, V2 and V3, and S over the left precordium appear late. Vectorcardiography, and radiological studies help in the detection of early or slight right cardiac enlargement.

In the *third phase*, a heart disease of pulmonary origin, symptoms and signs of myocardial failure, appear and threaten dissolution within a few years. The development of pulmonary hypertension and polycythemia adds to the loudness and splitting of the P2 sound and gradually leads to the appearance of signs of right heart failure, engorged neck veins, cyanosis, enlarged liver, ascites, and edema, all of which are rather late findings. Supportive treatment, coronary vasodilators, and cardiac tonics are usually effective, for a time at least, even in this stage of chronic pulmonary disease.

However, the diagnosis and the developing cardiopulmonary process should be made in its incipiency long before symptoms develop and steps taken to postpone the progression by prompt early vigorous treatment of the pulmonary condition. Unfortunately, the majority of patients do not present themselves until the disease is far advanced. We must be alert to the facts that every worker in a dusty trade, every asthmatic patient, every person with recurrent bronchitis, bronchiectasis, fibrosing tuberculosis, pneumonitis, sarcoidosis, bronchopulmonary disease of spirochetal, parasitic a protozoal origin, repeated sprays of pulmonary embolism[13] or cystic disease of the lung may develop primary cor pulmonale.

Secondary cor pulmonale results from capillary engorgement, alveolar edema in valvular disease as develops in mitral stenosis and in Eisenmengers complex or pulmonary valvular disease. It is necessary to rule out the presence of signs of constrictive pericarditis, or valvular disease and coronary artery lesions which may be obscured by progressive emphysema,[14] and masquerade as heart disease of pulmonary origin.

SUMMARY

1. Criteria for definite, pure, chronic cor pulmonale have been set down and 51 patients who meet these qualifications were studied. By far, the greatest incidence is in middle aged white males, though it is seen in all ages, both sexes, and in various racial groups.

2. The electrocardiogram shows the changes rather late, and in general was of relatively little value in assessing the degree of cardiac change; yet, the ecg. finding may be the first to focus attention on the presence of a right ventricular overload.

3. Detailed blood volume studies were done in 17 patients with cor pulmonale and six individuals with emphysema, using isotopes I_{131} human serum albumin to determine plasma volume, and Cr_{51} for estimation of the total red blood cell mass. The emphysema patients were not consistently abnormal, but those with definite cor pulmonale showed a variable increase of total blood volume, and a consistent increase of red blood cell mass.

4. Follow-up studies after digitalization of patients with failure showed decrease in plasma volume invariably, and frequently, a marked inexplicable decrease of red blood cell mass.

5. In management of these patients, we have strongly emphasized the importance of prophylaxis, early recognition, and energetic treatment in the early phases, even before cardiac changes are manifest. We must admit that the patients who have met our criteria represent the most advanced and refractory ones. While the long term prognosis is poor, current drugs and practices offer the patient comfort, ability to work, and probably a longer life span than was previously possible.

RESUMEN

1. Un criterio definido y puro sobre el cor pulmonale crónico se ha establecido ye se han estudiado 51 enfermos que reunieron las características. La mayor incidencia, con mucho, se encuentra en los hombres de

mediana edad, aunque se ve todas las edades en ambos sexos y en varios grupos raciales.

2. El electrocardiograma muestra los cambios más bien tarde y en general fué de escaso valor para estimar el grado de la alteración cardiaca; sin embargo puede ser que ECG por sus cambiossea el primero que llame la atención sobre la presencia de abolsamiento del ventrículo derecho.

3. Se hicieron estudios detallados de volumen sanguíneo en 17 enfermos con cor pulmonale y en seis individuos con enfisema, usando seroalbúmina marcada con I_{131} para determinar volumen plasmático y Cr-51 para la estimación de la masa celular total de eritrocitos. Los enfermos de enfisema no fueron siempre anormales pero aquéllos con cor pulmonale definido mostraron un aumento variable en el volumen total sanguíneo y consistente aumento de la masa celular de eritrocitos.

4. El seguimiento de los enfermos después de digitalización con desfallecimiento mostró decrecimiento de volumen del plasma invariablemente y frecuentemente, un inexplicable decrecimiento del volumen celular de eritrocitos.

5. En el tratamiento de estos enfermos hemos recalcado fuertemente la importancia de la profilaxis, descubrimiento rápido, y tratamiento enérgico de modo temprano aún antes de que haya alteraciones cardiacas.

Debemos admitir que los enfermos que reunieron las características según nuestro criterio representan los más avanzados y refractarios.

Si bien el pronóstico a la larga es malo, las drogas actuales y los métodos ofrecen al enfermo confort, capacidad de trabajo y probablemente una prolongación de la vida mayor de lo que era posible antes.

RESUME

1. L'auteur a déterminé les critères qui permettent de définir le coeur pulmonaire chronique pur, et a étudié 51 malades qui entrent dans cette catégorie. La fréquence la plus grande est de loin celle des individus de sexe masculin, de race blanche, moyennement âgés, encore que cette affection soit constatée à tous les âges, dans les deux sexes, et chez divers groupes raciaux.

2. L'électrocardiogramme montre des altérations plutôt tardives et n'a en général que peu de valeur pour déterminer l'importance de l'altération cardiaque; toutefois les constatations électrocardiographiques peuvent être les premières à signaler l'existence d'une anomalies ventriculaire droite.

3. Des études détaillées sur le volume sanguin furent faites chez 17 malades atteints de coeur pulmonaire, et six atteints d'emphysème, avec détermination du volume plasmatique et évaluation de la masse totale des globules. Les malades atteints d'emphysème ne montrèrent pas constamment des anomalies, mais ceux qui étaient atteints de coeur pulmonaire montrèrent une augmentation variable du volume sanguin total, et une augmentation importante de la masse des globules rouges.

4. Des contrôles après traitement des malades par la digitaline suivi d'échec, montrèrent invariablement une diminution du volume plasmatique et fréquemment une nette et inexplicable diminution de la masse des globules rouges.

5. Dans la conduite du traitement de ces malades, l'auteur insiste fortement sur l'importance de la prophylaxie, de la découverte précoce de l'affection et d'un traitement énergique dans la phase de début, avant même que des altérations cardiaques ne se soient manifestées. On doit admettre que les malades qui répondent aux critéres que l'auteur a proposés reprèsentent les cas les plus avancés et les plus sérieux. Bien que le pronostic à long terme soit mauvais, les drogues et médications courantes permettent d'offrir au malade un certain bien-être, la possibilité de travailler, et probablement une survie plus longue que celle qui était auparavant possible.

ZUSAMMENFASSUNG

1. Es wurden Merkmale niedergelegt für ein fest begrenztes reines chronisches cor pulmonale und 51 Kranke untersucht, auf die diese Kennzeichnung zutraf. Das bei weitem häufigste Vorkommen liegt bei weissen Männern im mittleren Alter, wenngleich man es in jedem Alter, bei beiden Geschlechtern und bei verschiedenen Rassen sieht.

2. Das Elektrocardiogramm zeigt die Veränderungen ziemlich spät und erwies sich im allgemeinen als von relativ geringem Wert bei der Bestimmung des Grades der cardialen Veränderung; der EKG-Befund kann den ersten auf den Brennpunkt gerichteten Augenmerk für das Bestehen einer Überbeanspruchung des rechten Ventrikels sein.

3. Ins Einzelne gehende Untersuchungen der Blutvolumina wurden an 17 Patienten mit cor pulmonale und 6 Personen mit Emphysem vorgenommen unter Verwendung von mit I_{131} markiertem menschlichen Serum-Albumin zwecks Bestimmung des Plasma-Volumens und von Cr_{51} zur Abschätzung der gesamten roten Blutzellmenge. Die Kranken mit Emphysem waren nicht durchweg abnormal, doch zeigten diejenigen mit ausgeprägtem cor pulmonale eine variable Zunamhe des gesamten Bluvolumens und eine damit übereinstimmende Zunahme der roten Blutzellmenge.

4. Nachuntersuchungen nach Digitalisierung von Kranken mit Versagen des Herzens zeigten eine gleichbleibende Abnahme des Plasma-Volumens und häufig eine ausgeprägte unerklärliche Abnahme der roten Blutzellmenge.

5. Hinsichtlich der Behandlung dieser Patienten haben wir besonders hervorgehoben die Wichtigkeit der Prophylaxe, frühzeitigen Erkennung und tatkräftigen Behandlung in den frühen Phasen, sogar ehe noch cardiale Veränderungen manifest werden. Wir müssen einräumen, dass die Patienten, auf die unsere Kriterien zutreffen, besonders weit fortgeschrittene und refraktäre waren. Während die Prognose auf lange Sicht schlecht ist, bieten doch die üblichen Mittel und Verfahren für den Kranken Erleichterung, Arbeitsfähigkeit und wahrscheinlich eine längere Lebensspanne als dies zuvor möglich war.

REFERENCES

1 Waltzer, L. and Frost, T. T.: "Cor Pulmonale: A Consideration of Clinical and Autopsy Findings," *Dis. Chest.*, 26:192, 1954.

2 Cournand, A.: "The Fourth Walter Wile Hamburger Memorial Lecture, Institute of Medicine of Chicago. Some Aspects of the Pulmonary Circulation in Normal

Man and in Chronic Cardiopulmonary Diseases—Andre Cournand," *Circulation*, 2:641, 1950.

3 Flint, F. J.: "Cor Pulmonale Incidence and Etiology in an Industrial City," *Lancet*, 267:51, 1954.

4 Scott, R. C., Kaplan, S., Fowler, N. O. Jr. and Stiles, W. J.: "ECG Pattern of RVH in Chronic Cor Pulmonale," *Circulation*, 11:927, 1955.

5 Herrmann, G. R.: *Diseases of the Heart and Arteries*, C. V. Mosby Company, St. Louis, 1952.

6 Reilly, W. A., et al: "Whole Blood Volume Determined by Radio Chromium Tagged Red Cells," *Circulation*, 9:571, 1954.

7 Lewis, C. S., Jr., Samuels, A. J., Daines, M. C. and Hect, H. H.: "Chronic Lung Disease, Polycythemia and Congestive Heart Failure. Cardiorespiratory Vascular and Renal Adjustments in Cor Pulmonale," *Circulation*, 6:874, 1952.

8 Sterling, K. and Gray, S. J.: "Determination of Circulating Red Cell Volume in Man by Radioactive Chrominum," *J. Clin. Inves.*, 29:1614, 1950. Read, R. C.: "Studies of Red-Cell Volume & Turnover Using Radio-Chromium: Description of a New 'Closed Method of Red-Cell-Volume Measurement'," *New England J. Med.*, 250:1021, 1954.

9 Crispell, K. R., Porter, B. and Nieset, R. T.: "Studies of Plasma Volume Using Human Serum Albumin Tagged with Radioactive I_{131}," *J. Clin. Inves.*, 29:513, 1950.

10 Miller, W. F.: "A Physiologic Evaluation of the Effects of Diaphragmatic Breathing Training in Patients with Chronic Emphysema," *Am. J. Med.*, 14:471, 1954.

11 Coy, J. E., Carroll, D. G. and Riley, R. L.: "Respiratory Acidosis in Patients with Emphysema," *Am. J. Med.*, 17:447, 1954.

12 Fulton, R. M.: "The Heart in Chronic Pulmonary Disease," *Quart. J. Med.* (New Series), 22:43, 1953.

13 Barr, J. R. and Knox, F. H., Jr.: "Embolic Obstruction of Major Pulmonary Arteries Producing Chronic Cor Pulmonale," *Dis. Chest*, 29:225, 1956.

14 Wasson, W. W.: *The Auxiliary Heart*, Charles C Thomas, Springfield, 1954.

The Fate of the Internal Mammary Artery Implant in the Ischaemic Human Heart

ARTHUR VINEBERG, M.D., F.C.C.P. and G. C. McMILLAN, M.D.
Montreal, Canada

The surgical treatment of coronary artery insufficiency by internal mammary artery implantation was attempted at McGill University in the animal first in 1945[1] and in man at the Royal Victoria Hospital in April 1950.[2]

The use of the pericardial fat pad graft to supplement the implant operation was first performed at the Royal Victoria Hospital in October 1953[3] on a human case of coronary artery insufficiency.

During the past 11 years much experimental evidence has been gathered to show that when an internal mammary artery is placed in the left ventricular myocardium it grows arteriolar branches which anastomose with the vast arteriolar network surrounding it within the myocardium of the left ventricle (Fig. 1A and B[4, 5, 6, 7, 8]).

These mammary-coronary anastomoses are extensive and, through them, fresh arteriolar blood is sent into the myocardium in sufficient quantity to relieve myocardial ischaemia caused by artificially produced coronary artery insufficiency.[9]

It has been repeatedly pointed out in previous publications that mammary-coronary anastomoses of large size have occurred in 46 per cent of implants placed and left in normal dog hearts, whereas, when the implanted internal mammary was left in dog hearts made ischaemic by partial ligation, or by sclerosing cellophane wrap of the anterior descending artery, the mammary-coronary rate has risen to 71 per cent.

Our experimental evidence has been confirmed in other centres when it has been carefully repeated.

There have, however, been disturbing reports concerning the failure of the internal mammary artery to anastomose with the coronary arteriolar tree in the experimental animal. In 1955 Bailey and Likoff[10] reported occlusion of implanted internal mammary arteries by thromboses. In our laboratory thrombosis of the implanted internal mammary artery has been rarely seen since 1946. Early in our experience we found that rough handling of the artery or tearing of the intercostals during separation of the artery from the chest wall favored thrombosis of the vessel. The Bailey-Likoff report was followed by Neptune[11] working with Bailey, who found mammary coronary arteriolar anastomoses in only 16.6 per

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From the Department of Surgery, Royal Victoria Hospital, and the Department of Pathology, McGill University.

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TABLE I

INTERNAL MAMMARY ARTERY IN NORMAL ANIMAL HEARTS 13 MONTHS TO TWO YEARS FIVE MONTHS AFTER IMPLANTATION

Animal Number	Time After Implantation	Histological Estimation Of Patency Per Cent	Size of Lumen Diameter
306-32	2 Years 5 Months	18	0.32 mm.
310-1A$_1$	2 Years 5 Months	5	0.32 mm.
356-78	1 Year 8½ Months	25	0.5 mm.
368-119B$_2$	1 Year 3½ Months	10	0.2 mm.
6	1 Year 1 Month	40	0.6 mm.

cent of animals undergoing internal mammary artery implantation. However, in his series there were only two of the 18 animals in whom the artery was thrombosed. It should be noted that Neptune's animals were studied after the artery had been left nine months in a normal non-ischaemic ventricular myocardium.

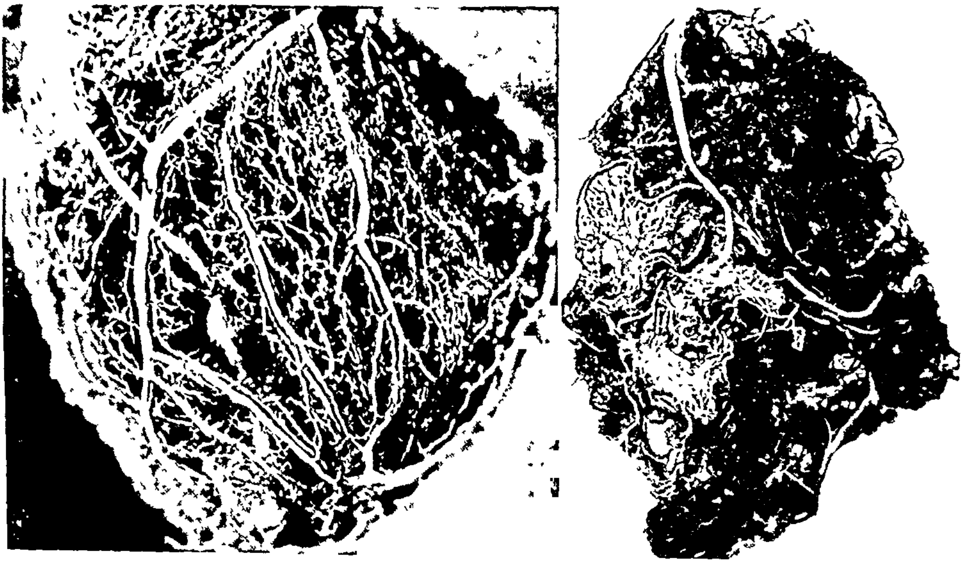

FIGURE 1A FIGURE 1B

Figure 1A: Digestion cast of implanted internal mammary artery made 12 days after implantation. Observe the fine arterial buds in tunnel.—*Figure 1B:* Digestion cast of implanted internal mammary artery made 7 months after implantation, and 5½ months after ligation of anterior descending branch left coronary artery (128B$_1$). Measurement of diameter of casted mammary artery and arterial lumina by dissecting microscope:

Internal mammary artery		
	at entrance to heart	2.25 mm.
	before branching	2.0 mm.
(Total of 7 branches)	after branching	1.5 mm.
Anterior descending branch left Coronary artery		2.25 mm.

More recently Bakst *et al* and Bailey[12] have studied internal mammary arteries six months after implantation into normal dog hearts. Backflow studies made on the anterior descending branch of the left coronary artery indicated that the internal mammary artery in their animals failed to augment the collateral circulation. The authors concluded that: "It has become strikingly obvious that in these experiments the internal mammary artery implant failed to contribute any measurable amount of blood to the anastomotic flow of the left anterior descending artery. It was further obvious that the collateral blood flow from the left anterior descending artery originated almost entirely in the unoccluded left circumflex despite the presence of a patent internal mammary implant."

This statement is most misleading, particularly in the light of a second statement by the same author two paragraphs later in the same article: "In each of these specimens an obliterative endarteritis largely occluded the lumen of the implanted vessel within a period of six months. It was obviously impossible for a physiologically significant quantity of blood to flow through these vessels."

It is difficult to understand how Bakst *et al* and Bailey expected that their internal mammary implants would contribute blood to the myocardium when they were almost completely blocked. The results reported by these authors differ greatly from those obtained in our laboratory for two major reasons. *The first of these is technical. It is perfectly obvious* from the published drawings that although the authors mention the

TABLE II

DIGESTION CAST STUDIES OF INTERNAL MAMMARY ARTERIES IN ISCHAEMIC HEARTS FIVE, SIX, AND SEVEN MONTHS AFTER IMPLANTATION

(All vessels measured by dissecting microscope)

			Internal Mammary Artery Diameter		
Number	Anterior Descending Diameter	Circumflex Diameter	Entrance Heart	Myocardial Tunnel Before Branching	After Branching
33W	1.1 mm.	1.0 mm.	1.3 mm.	1.0 mm.	0.5 mm.
$128B_1$	2.25 mm.	....	2.25 mm.	2.0 mm.	1.50 mm. Total 7 branches
521B	1.0 mm.	1.75 mm.	1.5 mm.	1.25 mm.	0.75 mm.
504	1.75 mm.	1.5 mm.	1.25 mm.	0.75 mm.	0.75 mm. Many branches
14W	1.25 mm.	1.0 mm.	1.5 mm.	1.25 mm.	0.75 mm. 3 branches
1F	1.25 mm.	....	1.12 mm.	1.12 mm.	1.0 mm.

Note small difference between size of internal mammary artery outside heart and in tunnel.

Most arteries were as large as anterior descending at its origin.

All animals survived anterior descending branch ligation 6 weeks after implantation.

TABLE III

STUDY OF SEVEN HUMAN INTERNAL MAMMARY ARTERIES 60 HOURS TO 18 MONTHS AFTER IMPLANTATION

		Per Cent
Total number of cases	7	
Number of patent arteries	6	85.8
Number of thrombosed arteries	1	14.2

(Arteries examined from 60 hours to 18 months after implantation)

avoidance of angulation of the internal mammary artery, they were unaware of the importance of making the myocardial tunnel so that it is in line with the point of the artery's attachment to the sternum (Fig. 2). Failure to observe this technical point causes angulation of the artery at

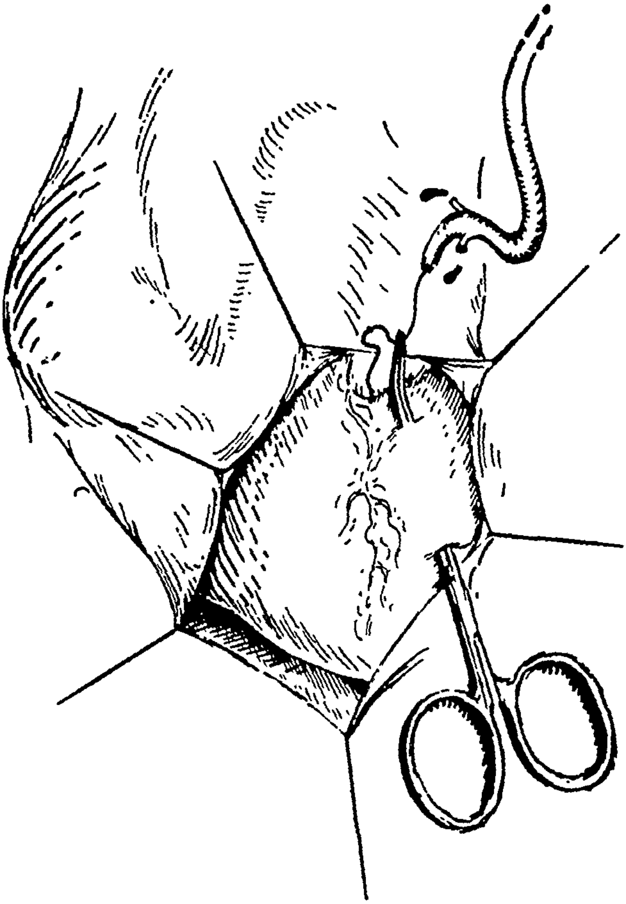

FIGURE 2: Reproduction of drawing published by Bakst *et al* and Bailey, of internal mammary artery implant. *Note* how direction of tunnel is placed in different plane to internal mammary artery on chest wall, which favours angulation, narrowing, and final obliteration of implanted vessel.

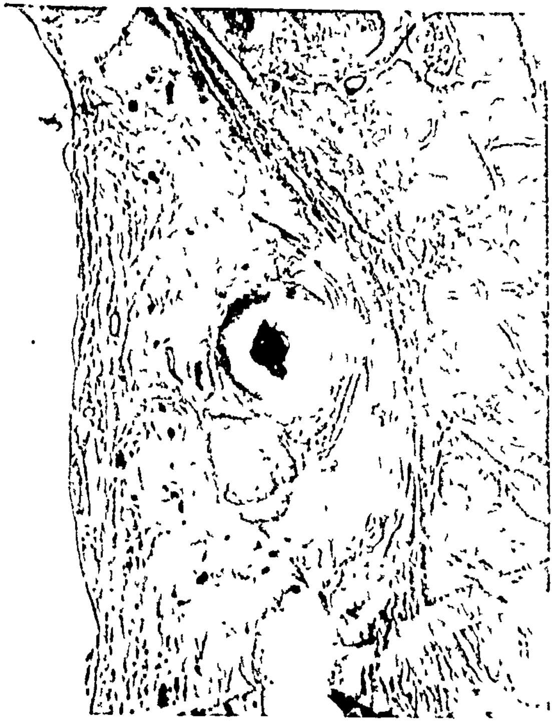

FIGURE 3A

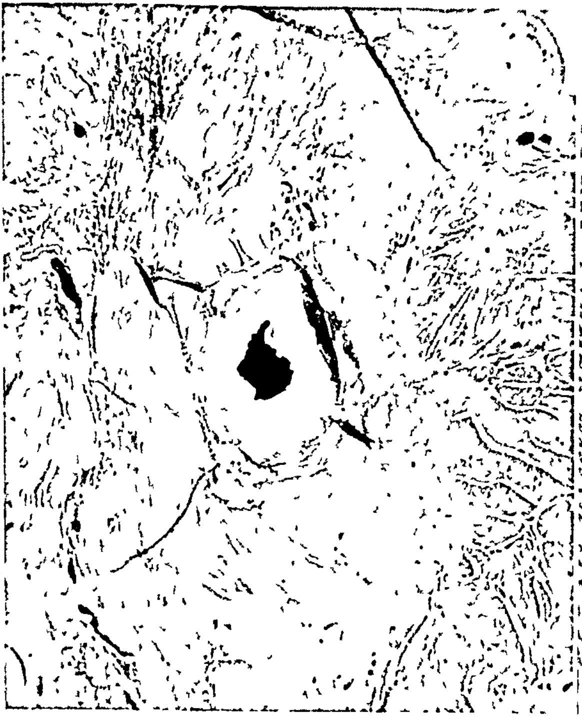

FIGURE 3B

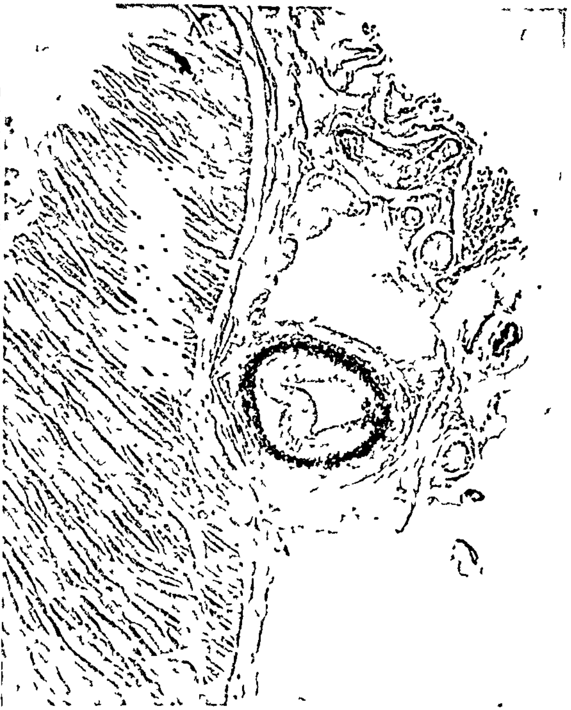

FIGURE 3C

Figure 3A: Microphotograph of animal No. 306, section 32 of internal mammary artery left in normal canine heart 2 years 5 months. Lumen 18% open, measuring approximately 0.4 mm.—*Figure 3B:* Microphotograph of animal No. 356, section 78 of internal mammary artery left in normal canine heart 1 year 8½ months. Artery lumen 25% open, measuring approximately 0.5 mm. —*Figure 3C:* Microphotograph of animal No. 6, 13 months after implantation into normal heart. *Note* 40% arterial lumen, measuring approximately 0.6 mm. at entrance to heart.

TABLE IV

OPERATIVE MORTALITY—INTERNAL MAMMARY ARTERY IMPLANTATION IN THE TREATMENT OF CORONARY ARTERY INSUFFICIENCY

		Per Cent Mortality
Total number of cases	54	
Angina decubitus—15 cases with 9 deaths		60
No angina at rest—39 cases with 3 deaths		7.6

The total deaths include the first patient operated upon in each of four different Montreal hospitals, all of which were cases of severe angina decubitus.

its point of entrance into the myocardium, resulting in arterial occlusion by thrombosis or intimal proliferation. Not only have these authors failed to follow the details of internal mammary implant technique frequently described by us, but they have failed to repeat carefully our experimental methods. Thus we find that the implanted internal mammary arteries described by Bakst *et al* and Bailey had been left in the myocardium of normal hearts. These implants were in competition with normal coronary arteries. Little wonder that they report the lumina of the implanted vessels were 95 per cent obliterated by severe intimal proliferation.

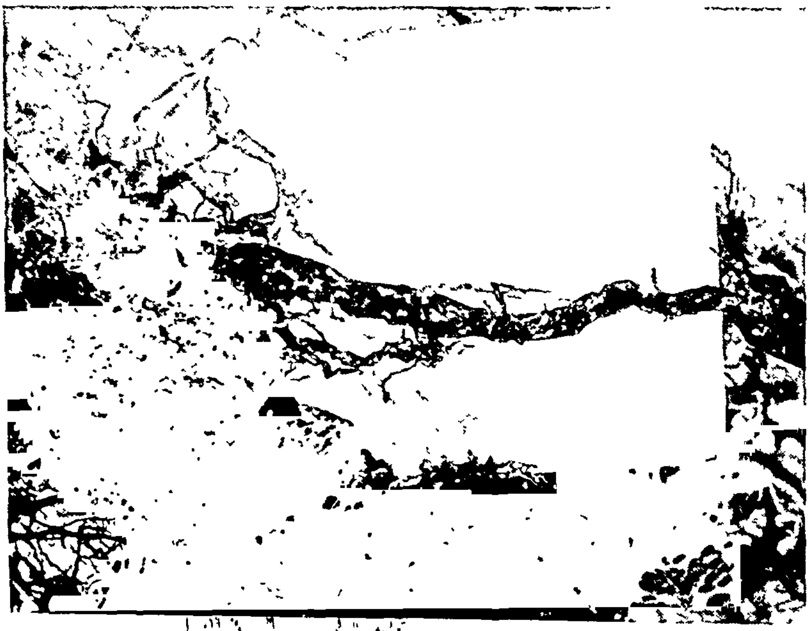

FIGURE 4: Digestion cast of internal mammary artery made 5 months after implantation and 4 months after anterior descending branch ligation. Measurements by dissecting microscope showed lumina as follows:

Anterior descending branch left Coronary artery		1.1 mm.
Circumflex		1.0 mm.
Internal mammary artery at		
	Entrance to heart	1.3 mm.
	before branching	1.0 mm.
	after branching	0.5 mm.

In our series, many hundreds of animals have been studied after internal mammary artery implantation. These can be divided into two groups, namely, those in which the artery was implanted and left in a normal non-ischaemic heart, and those in which the artery was implanted and left in an ischaemic heart. In the first non-ischaemic group, our implants developed intimal proliferation. Rarely, however, has there been the extensive intimal proliferation reported by Bakst *et al.* and Bailey. When it did occur, there was some mechanical factor, such as angulation, or a partial mural thrombus, which narrowed the internal mammary artery thus reducing the rate of blood flow through its channels and favouring intimal proliferation.

In the absence of arterial thrombosis or angulation it is true that intimal proliferation does occur, but rarely to the extent of obliterating 95 per cent of the arterial lumen. In Table I are listed five animals studied 13 months to two years five months after implantation. In all of these the internal mammary artery was left in a normal heart which did not need it and the arterial lumina remained from 10 to 40 per cent open. The largest lumen was 0.6 mm. and the smallest 0.2 mm. All showed mammary-coronary anastomoses. Certainly four out of five had lumina large enough to supply a helpful amount of blood to the left ventricle (See Fig. 3A, B, C).

In the second group of animals the internal mammary arteries were left in position for many months in hearts rendered ischaemic by ligation of the anterior descending artery branch six weeks after internal mammary implantation. The fate of the implanted internal mammary arteries left in seven ischaemic hearts is shown in Table III. Five, six and seven months later flow studies were made and the rate of blood flow through the implants determined.[9] Digestion casts of the cardiac circulation were

TABLE V

RESULTS OF CORONARY ARTERY INSUFFICIENCY TREATED BY INTERNAL MAMMARY ARTERY IMPLANTATION IN 49 PATIENTS FOLLOWED SIX MONTHS TO 5½ YEARS

	Before Operation					After Operation							
	Number of Patients	Totally Disabled		Survived		No Pain or Slight Pain		Less Pain		The Same or Worse		Returned to Work	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
No angina at rest	35	26	74.3	32	91.7	23	65.7	3	9.3	8	21.8	30	85.7
								—75%—					
Angina decubitus	14	14		7		3	21	1	7.1	3	21	4	28.5

5 patients with no angina at rest have died months to years after operation.
27 (77.1%) of this group are still alive; 23 (65.7%) have no pain or less pain.
27 (77.1%) still work.

made by injecting the internal mammary artery and coronary vessels with different coloured plastics. Using the dissecting microscope, the cast diameters of eight transplanted internal mammary arteries were measured at the entrance to the heart, and before and after branching. Note how the arteries maintain their lumina in six out of eight animals. The arteries were patent with small anastomoses in two. The internal mammary artery remained open in all eight animals (100 per cent).

A comparison between the diameter of the lumina of the anterior descending branch, circumflex, and internal mammary arteries as outlined by the casts made of them, is of interest. In three out of six, the diameter of the lumen of the internal mammary artery outside the heart was greater than the anterior descending branch of the left coronary at its origin. It was equal in one, and slightly less in two. There is slight reduction in the size of the internal mammary vessel after entrance into the myocardial tunnel, and marked reduction after it has given off its many new branches. In the casts the branches can be seen to join with arterioles of the myocardial arteriolar network.

These arteries were left in ischaemic myocardia. Obviously there was

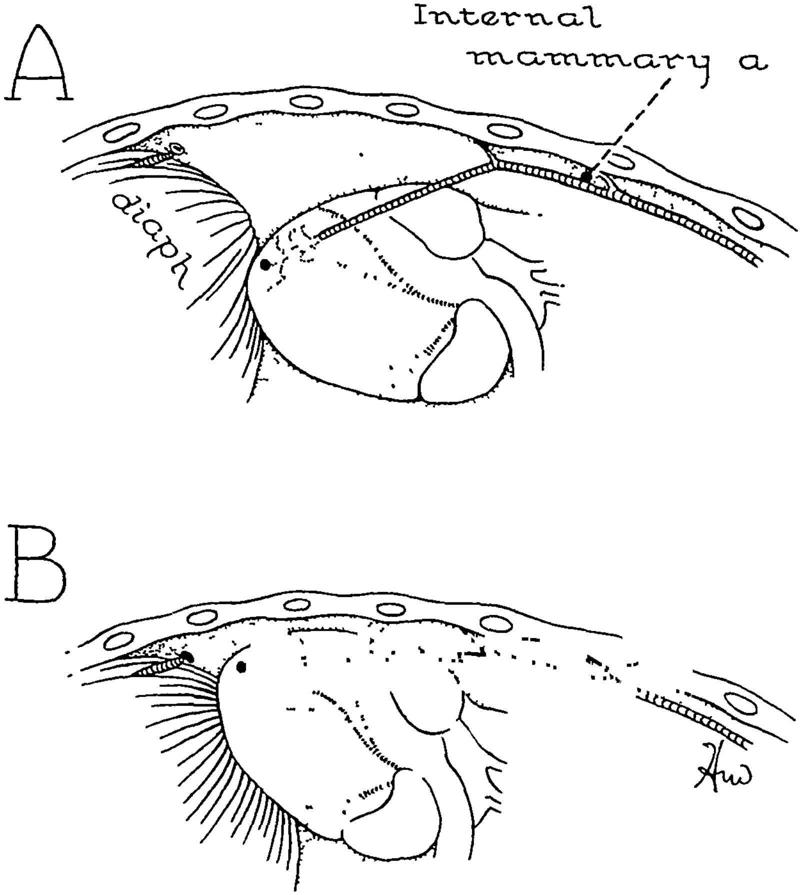

FIGURE 5. Method of placing internal mammary artery in tunnel

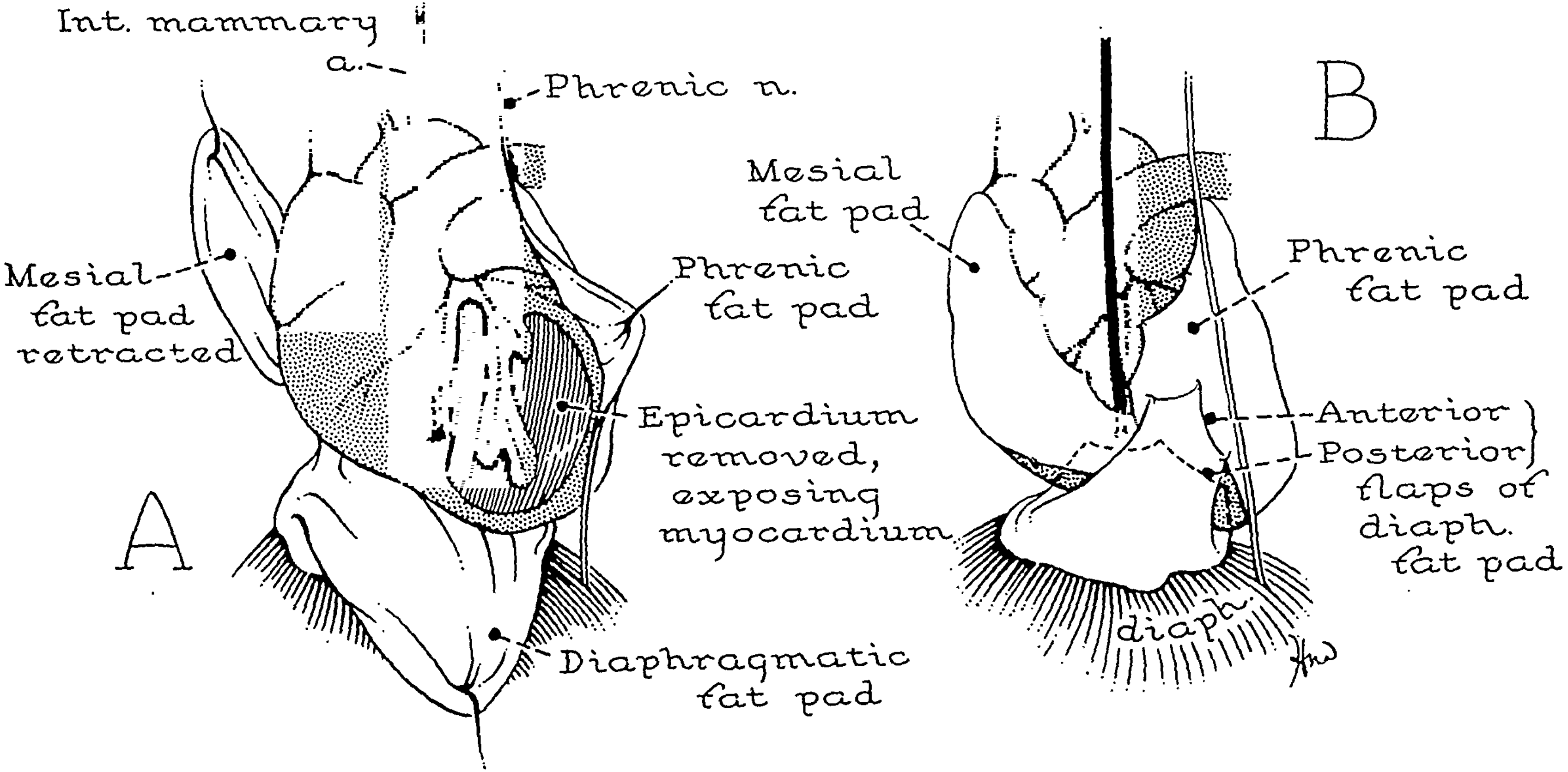

FIGURE 6: Technique of pericardial fat pad graft.

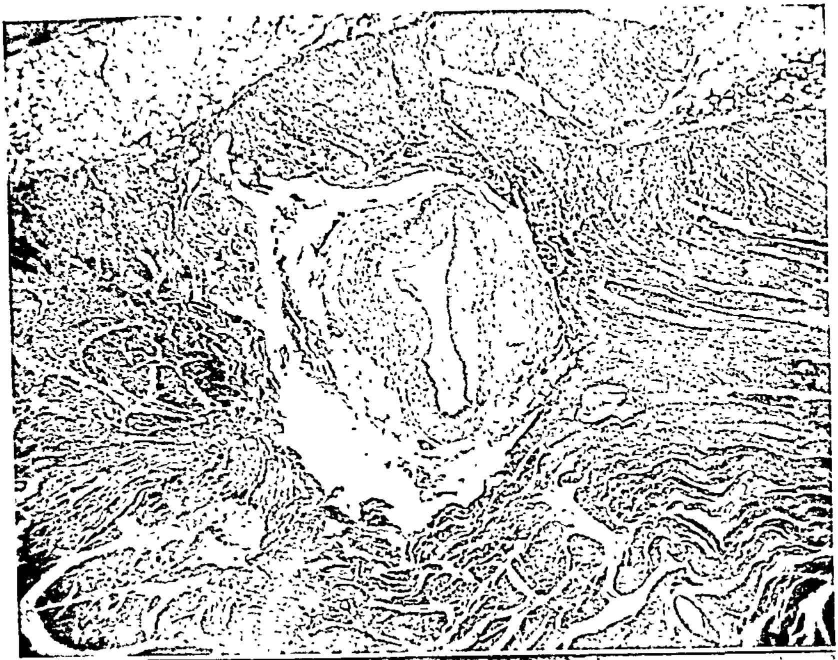

FIGURE 7

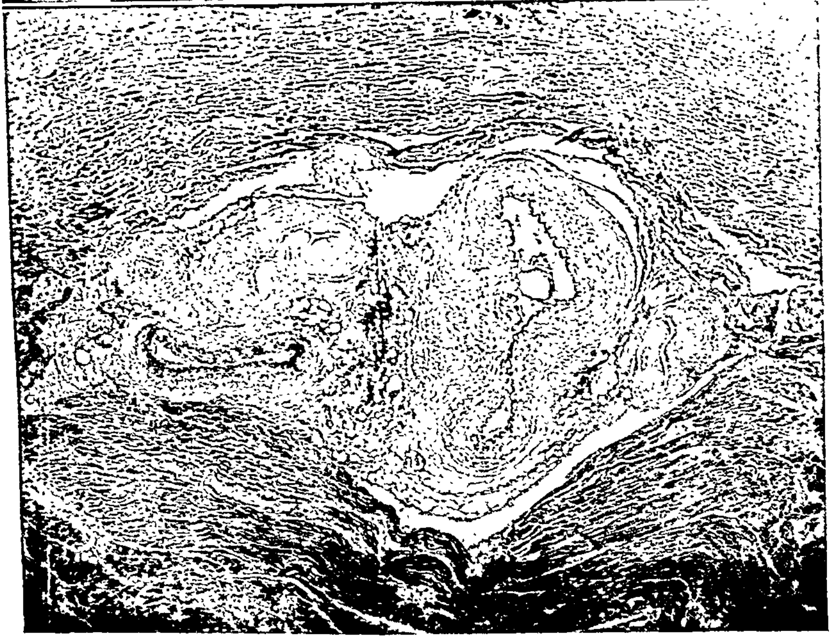

FIGURE 8

Figure 7: Microphotograph of human internal mammary artery lying within the myocardium 62 hours after implantation. *Note* open arterial lumen and absence of haematoma. There is little reaction surrounding the vessel other than a small zone of muscle necrosis.—*Figure 8:* Microphotograph of human internal mammary artery 60 hours after implantation with second vessel alongside of it—presumably the 6th intercostal artery. Again there is no haematoma, and there is a small area of muscle necrosis about the implant.

no marked obliteration of their lumina. The flow rate through these vessels has been published[9] and was satisfactory. In one animal (Fig. 4) it reached 55 cc. per minute, compared to a normal left coronary artery of cc. per minute in dogs of this size.

In the human suffering from severe anginal pain due to coronary artery disease, there is ischaemia of the ventricular myocardium. We have studied one example in which an internal mammary artery placed in this type of muscle had not been closed off by intimal proliferation when examined 18 months later.

In our series of 54 human patients operated upon for coronary artery insufficiency, we have studied at necropsy seven implanted human internal mammary arteries 60 hours to 18 months after implantation. A brief report of the pathological findings will be given but, before presenting the material, it might be well to briefly outline the operative procedure in order that the histological data may be more readily understood.

The Vineberg Operation for Coronary Artery Insufficiency

There has been little variation in the technique of internal mammary artery implantation since 1950.[13] The operation (Fig. 5) consists of freeing the left internal mammary artery from the chest wall by ligating and transecting the intercostal branches between the fourth and sixth interspaces inclusively. The internal mammary artery thus freed from the

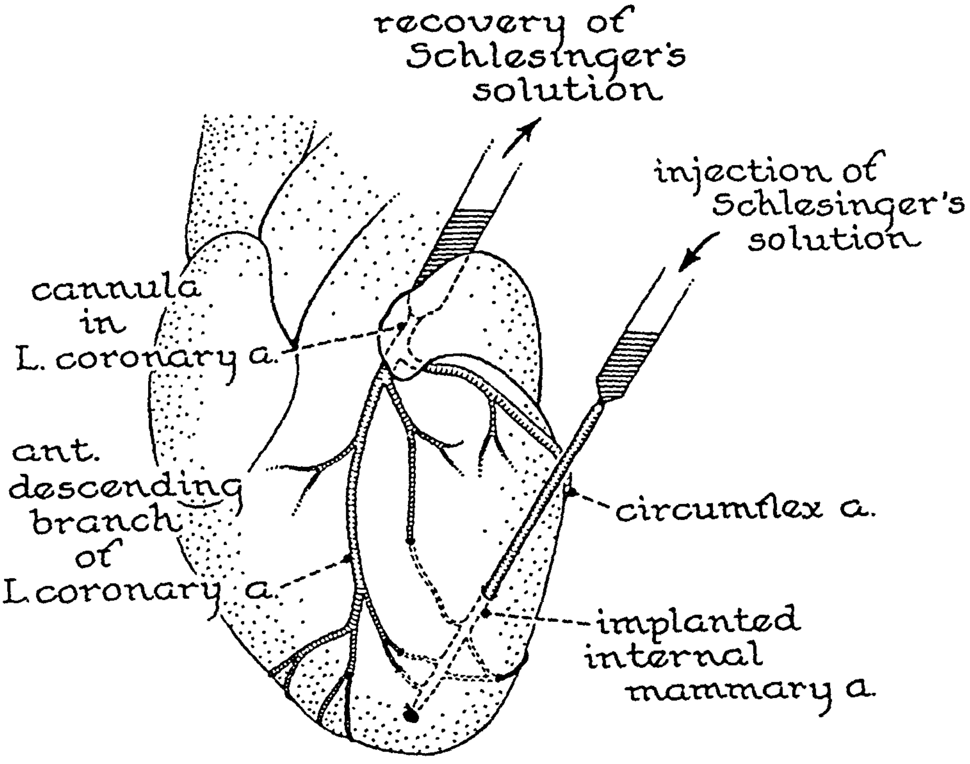
recovery of Schlesinger's solution
injection of Schlesinger's solution
cannula in L. coronary a.
ant. descending branch of L. coronary a.
circumflex a.
implanted internal mammary a.

FIGURE 9: Standard method of injecting internal mammary artery through cannula in internal mammary artery. Injection mass returns through cannula placed in left coronary artery.

chest wall is transected between two ligatures distal to the sixth interspace. The proximal free end of the artery is pulled into a tunnel made in the wall of the left ventricle. Before it is drawn into this tunnel, the sixth intercostal artery is cut so that blood escapes freely through it from the internal mammary artery into the surrounding myocardial tunnel. The open sixth intercostal or slit into the side of the internal mammary artery allows the blood to move down and out of the artery: the peculiar sponge-like character of the myocardial vessels assures that the blood which escapes from the implanted internal mammary artery is carried away. By this technique arterial blood reaches the myocardium immediately, and within three to four weeks through arteriolar mammary-coronary anastomosis. Slowing of the blood flow through the implanted vessel due to angulation or mural thrombus favors thrombosis and intimal proliferation. There is evidence to indicate that the extent of the intimal proliferation in the implanted vessel is directly proportional to the rate of blood flow through it.[13]

In October 1953 the standard Vineberg implant procedure was supple-

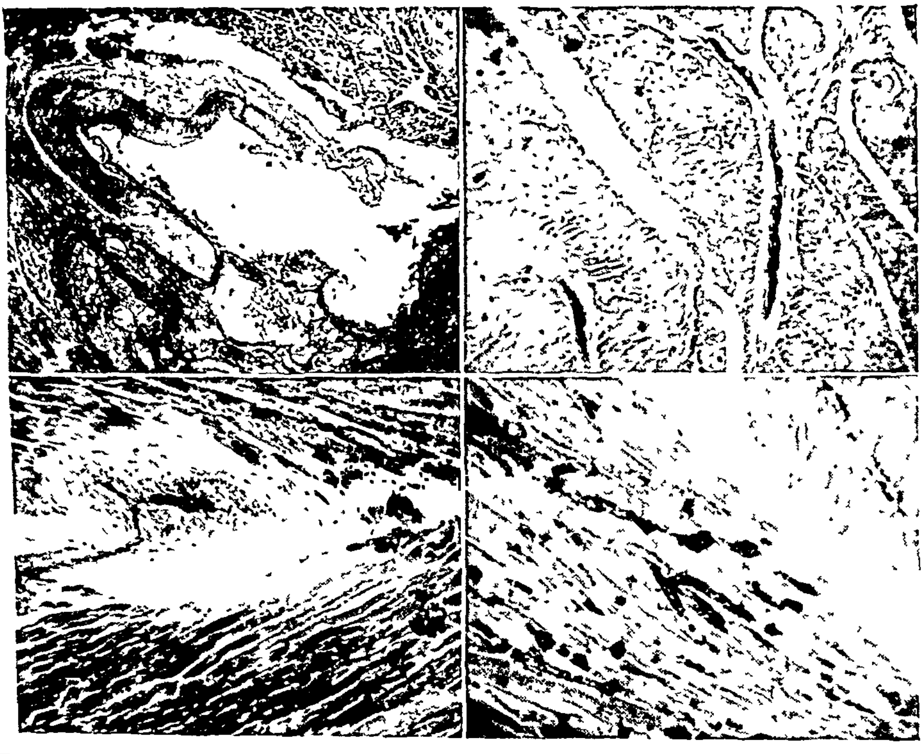

FIG. 10A

FIG. 10C

FIG. 10B

FIG. 10D

Figure 10A: Internal mammary artery in myocardium of human case of angina decubitus. This patient died 82 hours after implantation, from intractable bronchial spasm following penicillin injection. At autopsy, the internal mammary artery was injected with India ink. *Note* the slit in the arterial wall, with India ink in the space surrounding the vessel. There is no haematoma.—*Figure 10B: Note* India ink filling the arterioles within the myocardium distant to the implant.—*Figure 10C* and *D*. Same patient as in Figure 10A and B. C, note how the India ink is lying in large spaces between muscle bundle groups These may be myocardial sinusoids filled with India ink. D, note how the India ink injected through the internal mammary artery has reached the capillaries which lie between muscle fibres.

mented for the first time by pericardial fat pad grafts in a human case of coronary artery insufficiency.[3]

The technique of the pericardial fat pad graft is simple (Fig. 6). The mediastinal, diaphragmatic, and phrenic fat pads are reflected from the surface of the fibrous pericardium and left attached to their respective blood supply. The fibrous pericardium is removed over the entire antero-lateral and part of the posterior surfaces of the left ventricle. Following internal mammary artery implantation, various areas of the epicardium are removed by sharp dissection from the antero-lateral and posterior surfaces of the left ventricle. This denudes the myocardium so that the raw vascular surfaces of the pericardial fat pads are placed in direct contact with myocardial muscle fibers and the many vascular spaces lying between the muscle fibers and bundles. The value of the pericardial fat pad as a source of myocardial blood flow has been studied since that time in the experimental laboratory.* A report of that study is now being prepared: it would seem that the pericardial fat pad is capable of supplying blood to an ischaemic myocardium. In the seven cases about to be described, a careful study of the pericardial fat pad was made in one patient.

Case 1: 62 hours after internal mammary artery implantation. The first human case of coronary artery insufficiency to undergo internal mammary artery implantation was operated upon in April 1950. The patient, a 53 year old tailor, had been totally disabled for 36 months due to severe angina at rest, without exciting cause. A true case of angina decubitus, he had experienced both anterior and posterior wall infarctions. He made an excellent recovery from his operation but died suddenly 62 hours later. Autopsy showed that he had been living on a pin-point opening in the circumflex artery, which had become blocked by a fresh thrombus. A section through the site of implantation of the internal mammary artery is shown in Fig. 7. The implanted internal mammary artery was widely open. There was no evidence of haematoma in the myocardial tunnel about the implanted artery, even though the

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*Experimental Laboratory of the Montreal Heart Institute, and Department of Experimental Surgery, McGill University.

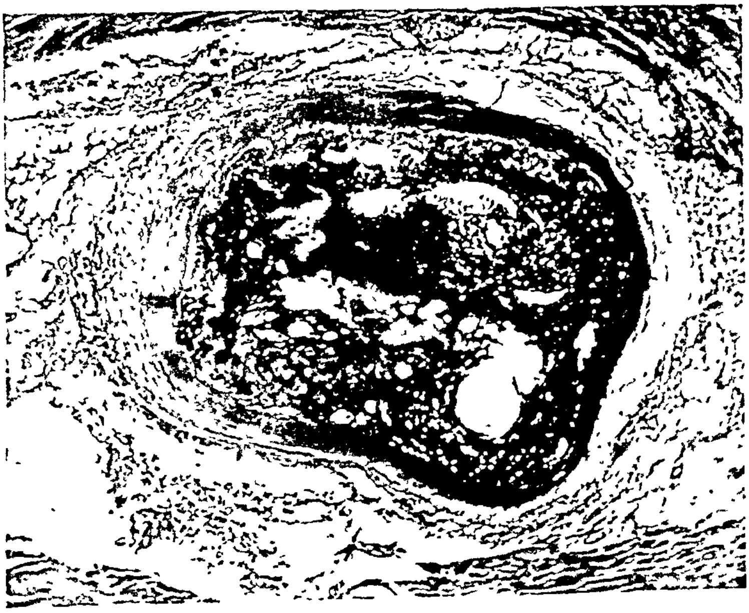

FIGURE 11: Microphotograph of internal mammary artery 96 hours after implantation into ischaemic heart. *Note* patent internal mammary artery containing India ink mixed with blood in its lumen.

artery had been placed in the tunnel with an attached bleeding sixth intercostal vessel. There was a small zone of myocardial muscle necrosis surrounding the vessel with little other reaction to the implanted vessel.

Case 2: 60 hours after internal mammary artery implantation. The second human internal mammary artery to be studied after implantation into the left ventricular myocardium was that of a 57 year old man. The patient, a civil servant, had been disabled for 36 months and, like our first patient, suffered angina at rest, without exciting cause. This second case of angina decubitus, like the first, had experienced both anterior and posterior wall infarctions prior to surgery. He, like the first patient, died suddenly 60 hours after operation from a fresh thrombus blocking a circumflex artery—apparently the only vessel open in his heart.

A section through the site of implantation is seen in Fig. 8. The internal mammary artery is widely patent, with a large patent artery alongside of it, presumably the sixth intercostal artery. There is no surrounding haematoma. There is a small area of muscle necrosis about the implant, similar to that seen in the first patient.

Case 3: 82 hours after internal mammary artery implantation. This 44 year old janitor, had been disabled by angina decubitus for four years, and had suffered both anterior and posterior left ventricular infarctions. He underwent operation successfully, but died 82 hours after implantation of the internal mammary artery and pericardial fat pad grafts. Death was caused by severe, intractable bronchial spasm which followed a penicillin injection three hours prior to his demise. At autopsy the internal mammary artery was injected with India ink proximal to its entrance into the myocardial tunnel (Fig. 9). This injection was made in the presence of a senior pathologist* who watched the coronary vessels of the left ventricle fill with the India ink injected through the internal mammary artery which had been implanted into the left ventricular myocardium 82 hours previously. There was no injection of the pericardial fat pad.

In this patient, just prior to pulling the internal mammary artery into the myocardial tunnel, the sixth intercostal had been cut but did not bleed satisfactorily. It was necessary to cut a hole in the wall of the internal mammary artery at the point of junction between it and the sixth intercostal vessel. This opening in the side wall of the implanted internal mammary artery is clearly visible in Fig. 10A. Apparently the India ink introduced into the internal mammary artery proximal to the heart left the artery through this hole and entered a larger space around the artery which had been created by spreading the muscle bundles when making the myocardial tunnel to receive the implant. From here the India ink had reached arteries (Fig. 10B), endothelial lined spaces between muscle bundles (Fig. 10C), and capillaries lying about muscle fibres (Fig. 10D). The exact mechanism of how this happens at this stage has not been proved to our satisfaction. However, it appears likely that the ink first escapes from the implanted internal mammary artery into the surrounding space created by the making of the myocardial tunnel. From this area it is carried to endothelial lined spaces lying between muscle bundles (Fig. 10C). These spaces may be the myocardial sinusoids described by Wearn[14] which are in communication with arterioles and capillaries.

Case 4: 96 hours after internal mammary artery implantation. A 60 year old man, was completely disabled for seven months because of angina decubitus following several coronary occlusions with infarction. In addition to this severe coronary artery insufficiency, he suffered from diabetes and hypertension. Four days after operation the patient, who had been doing well, died suddenly. Death was caused by a fresh thrombus occluding the right artery.

Examination of the implanted internal mammary artery showed it to be completely patent (Fig. 11). It should be noted that the narrow zone of necrotic myocardial muscle surrounding the implant is beginning to show healing and organization. Unfortunately, in this patient India ink was not injected into the implanted internal mammary artery as was done in our third case.

Case 5: 10 days after internal mammary artery implantation. This 44 year old man, had suffered two coronary artery occlusions, with infarction. He had experienced left-sided hemiplegia with almost complete recovery of the latter. His exercise tolerance was limited to two blocks because of anginal pain. He had been totally disabled for two years, but was not a case of angina decubitus. The post-operative course of this patient is important in the light of the findings at autopsy. He did not receive Wangensteen suction, although it is a routine procedure in all patients operated upon for coronary artery insufficiency. On the fourth post-operative day there was marked abdominal distension and vomiting due to paralytic ileus. It took three days to partially control this complication. On the 10th post-operative day he died suddenly from occlusion of the artery by a fresh thrombus. At autopsy the apex of the heart was elevated and displaced laterally by the raised diaphragm. This shift of the

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*Dr. Paul Mailloux, Senior Pathologist, Montreal Institute of Cardiology, Montreal, Canada.

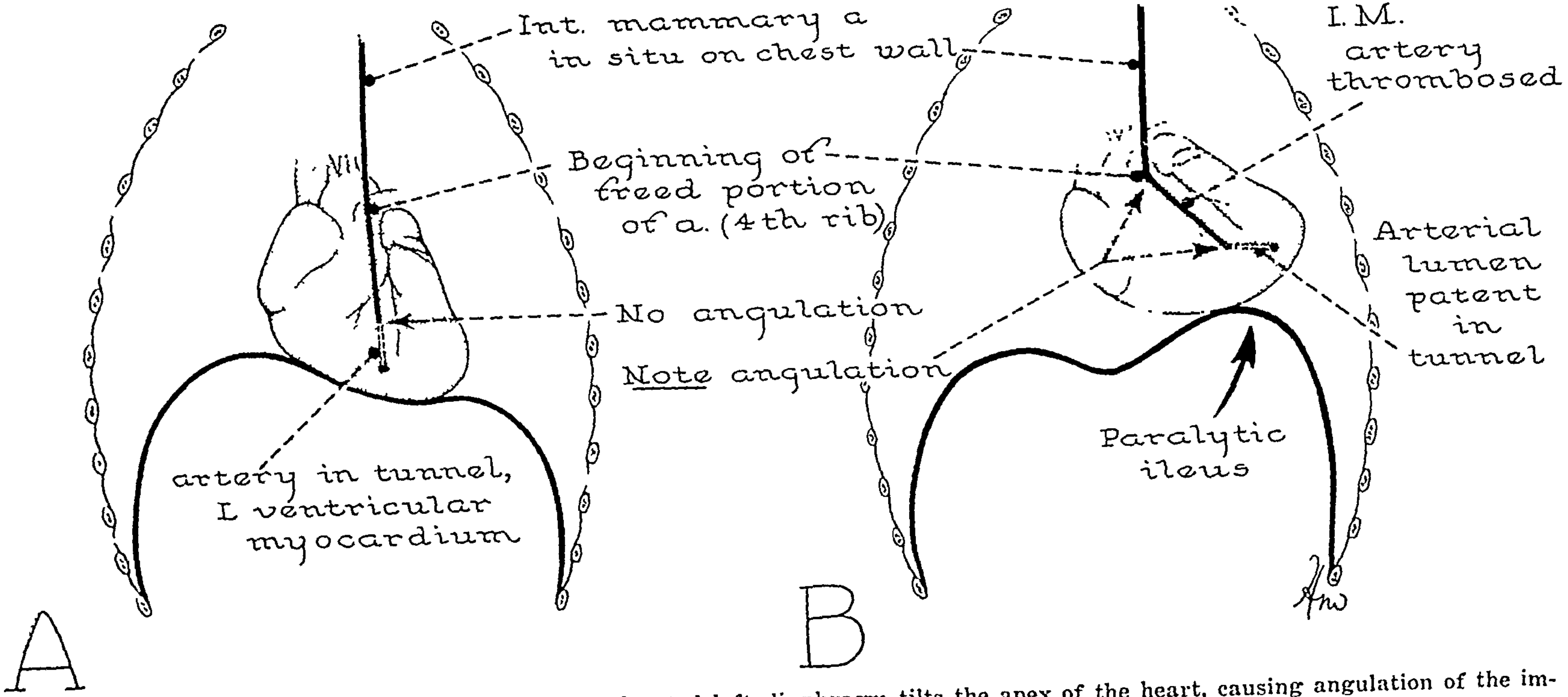


FIGURE 12: The above sketch indicates how the elevated left diaphragm tilts the apex of the heart, causing angulation of the implanted internal mammary artery. Angulation of artery resulted in thrombosis of vessel.

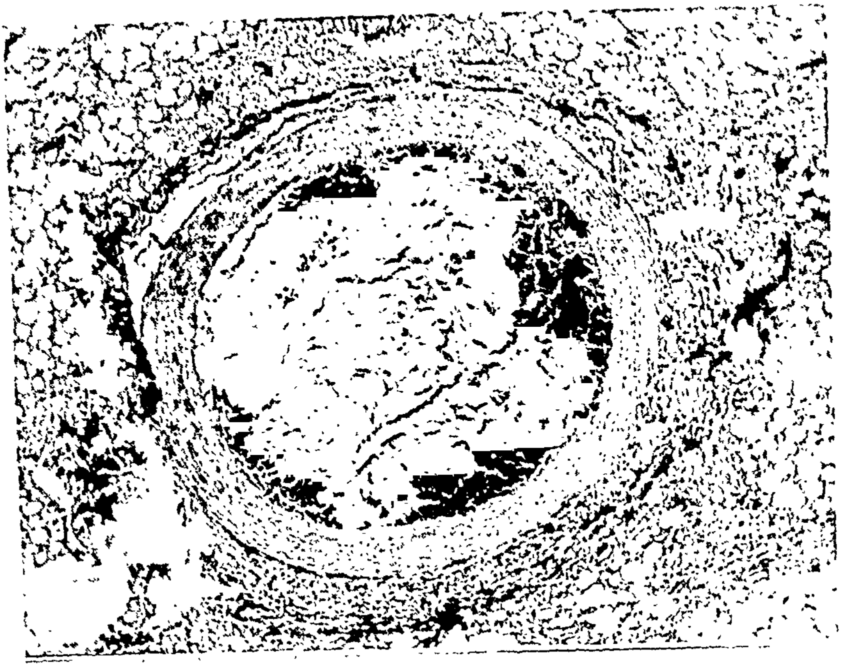


FIGURE 13

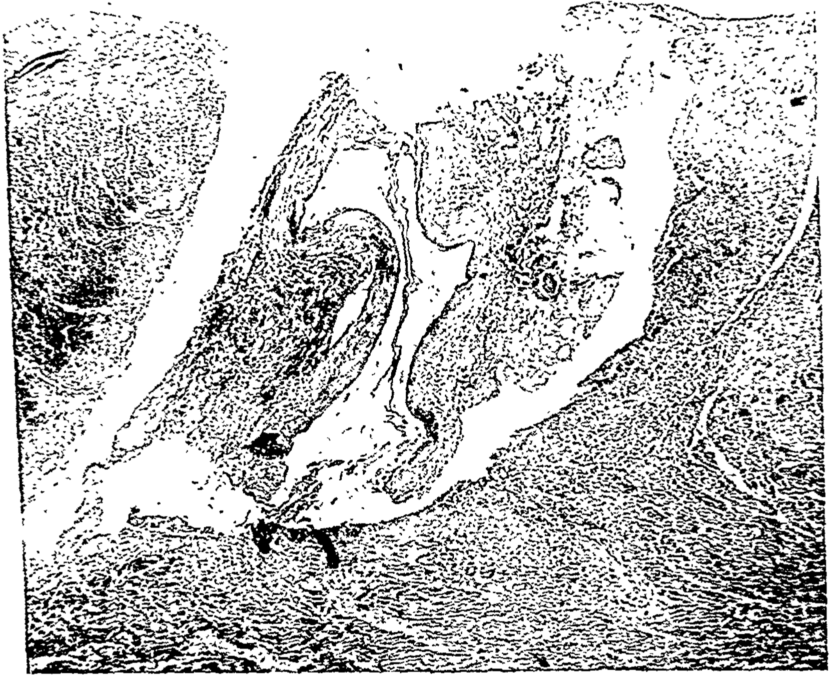


FIGURE 14

Figure 13: Microphotograph of human internal mammary artery 10 days after implantation, with 6 day old thrombus (estimated age) occluding its lumen. *Note* relationship between peak of paralytic ileus 4 days post-operative and estimated 6 day age of thrombus.—*Figure 14:* Microphotograph of section made through intramyocardial portion of same artery shown in Figure 13. *Note* artery in Figure 13 *outside* heart is thrombosed *due to angulation*, whereas same artery lying *in* heart shown above is patent.

FIGURE 15A

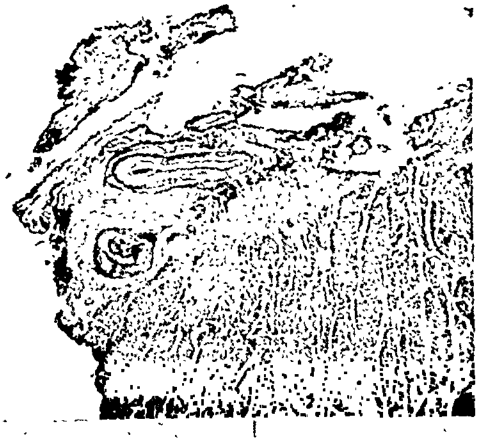


FIG. 15B

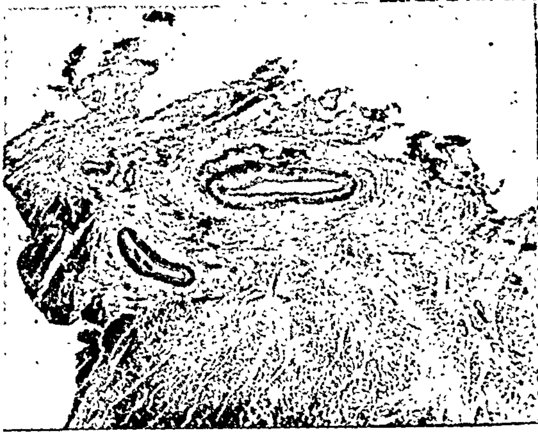


FIG. 15C

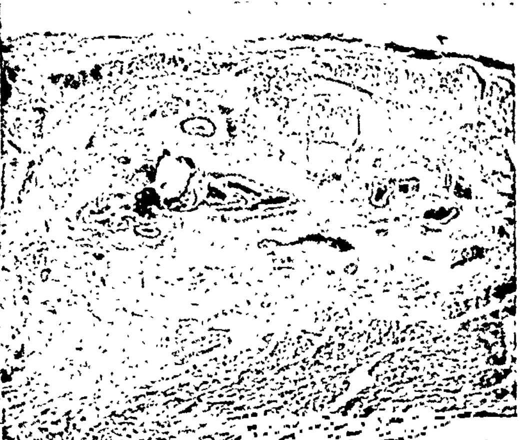


FIG. 15D

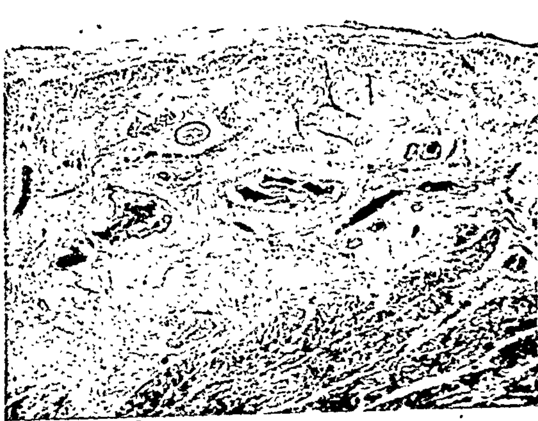


FIG. 15E

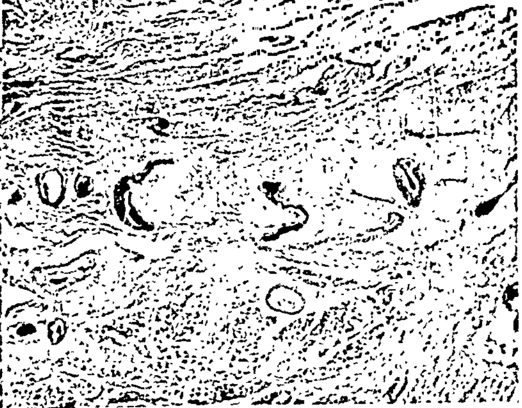


FIG. 15F

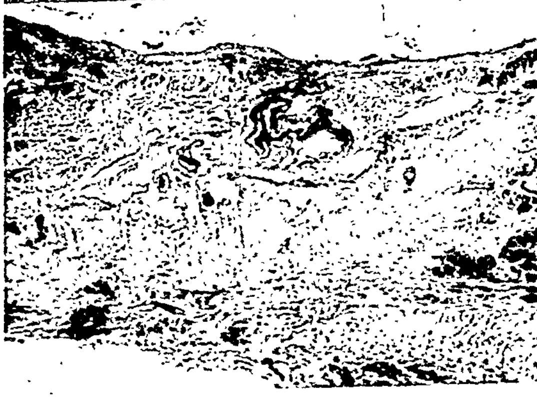
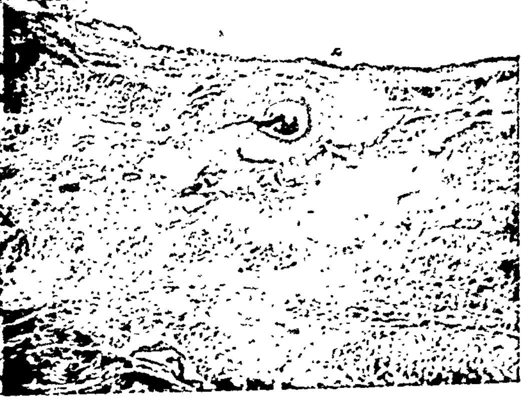


FIG. 15G



longitudinal axis of the heart into an almost transverse position in the thorax had resulted in acute angulation of the internal mammary artery at the chest wall and at its entrance into the heart (Fig. 12). The internal mammary artery was thrombosed (Fig. 13) in that portion proximal to its entrance into the heart. It was patent within the myocardial tunnel (Fig. 14). The duration of the thrombus was estimated, pathologically, to be not more than six days. It was four days after operation that the paralytic ileus, with abdominal distension and elevation of the left diaphragm, was discovered and treated. Six days later the patient died. Since the thrombus in the internal mammary artery was estimated to be not more than six days old, it is reasonable to assume that it developed as a result of the angulation brought about by the upward and left lateral displacement of the heart through abdominal distension. The clinical observation corroborates our frequently reported observations in animals concerning the disastrous effect of angulation on implanted internal mammary artery patency.

Case 6: 18 months after internal mammary artery implantation and pericardial fat pad graft. The last patient, a 60 year old aircraft worker, suffered from angina decubitus, requiring 300 nitroglycerine tablets per week. He had had two attacks of

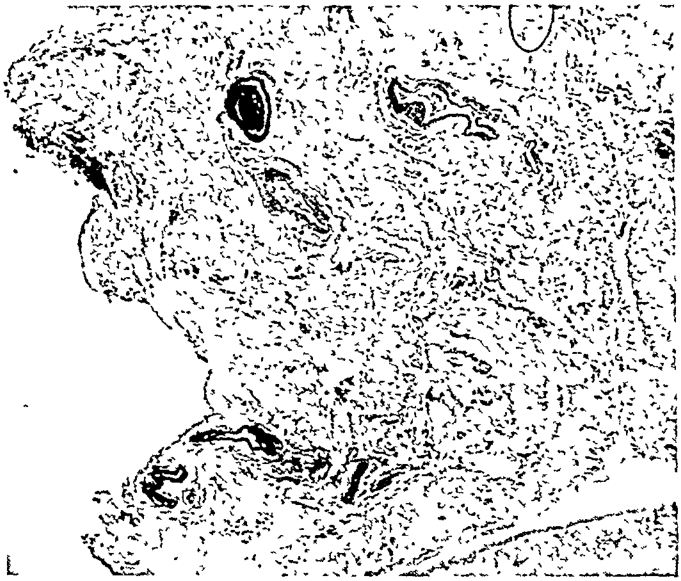


FIGURE 16: Microphotograph of pericardial fat pad graft showing injection of vessels with India ink from retrograde circumflex artery injection.

At left:

Figure 15: Microphotographs of serial sections taken through implanted human internal mammary artery 18 months after implantation.—*Figure 15A:* Before tunnel. Here the internal mammary artery is seen lying on the surface of the left ventricular myocardium. It is flattened due to deep-freeze packaging which resulted in flattening of the entire specimen. It is widely open and shows little or no intimal proliferation, and the lumen contains India ink which was injected through the circumflex artery.—*Figure 15B:* Entrance to Tunnel. The artery is seen at the beginning of the tunnel, widely open, with India ink in another myocardial vessel.—*Figure 15C:* First 1/4 of tunnel. Shows artery branching within the myocardium. The branches contain India ink. Again there is no evidence of intimal proliferation.—*Figure 15D:* First 1/3 of tunnel. In this area the artery breaks up into arteriolar branches and many almost cavernous-like cavities containing India ink.—*Figure 15E:* Centre of tunnel. The artery can no longer be identified. It has broken up into numerous branches containing India ink, and two vessel complexes one of which slowly disappears when followed through the tunnel. The other continues branching and eventually reconstitutes itself as an artery.—*Figure 15F:* Last quarter of tunnel. Here one sees the artery after reconstitution. It is open, still branching, and shows no evidence of intimal proliferation.—*Figure 15G:* End of tunnel. The artery is still open, and branching at the very end of the tunnel. It contains India ink which was injected, retrograde, through the circumflex artery.

coronary artery thrombosis with resultant antero-lateral and posterior wall infarctions. On November 18th, 1953, he underwent internal mammary artery implantation and pericardial fat pad graft. Four months after operation he was able to walk a distance of one to two miles without pain, and resumed his work as an aircraft worker on an eight-hour night shift. He continued in good health, experiencing only occasional substernal pain after marked effort. In may 1955 he developed intestinal obstruction and died. There was no evidence of cardiac disability. Death was due to cancer of the pancreas. The patient had requested that, after death, his heart be sent back to Montreal. It was received in a deep-freeze package. The internal mammary artery could not, at first, be identified, so India ink was injected into the circumflex artery in a retrograde manner. The internal mammary artery was then identified and was found to contain India ink, as did the diaphragmatic fat pad which had been placed on the myocardium at the time of operation 18 months before.

Over 800 microscopic serial sections of the implanted internal mammary artery, which had been left in an ischaemic human heart for 18 months, were studied. Through this study certain facts were definitely established. There was little doubt that this particular internal mammary artery had been implanted into an ischaemic human heart. There was diffuse myocardial fibrosis, and marked narrowing of all three major coronary vessels. The internal mammary artery had been implanted into a shallow one inch tunnel in the anterior wall of the left ventricle. The condition of the artery in the tunnel and its branches has been made clear as a result of the extensive serial section study made by the authors. Unlike the many arteries examined in our animal series, this human artery shows no intimal proliferation distal to its points of branching. It has a normal lumen throughout. Representative microscopic sections of the implanted internal mammary artery as it passes through the myocardial tunnel have been selected at different levels. Thus, in Fig. 15A, the internal mammary artery is seen lying on the surface of the left ventricle before entering the myocardial tunnel. It appears flattened due to squeezing of the entire specimen as the result of deep-freeze shipment. It should be noted that the lumen is almost completely normal and shows little intimal proliferation. It contains India ink, injected retrograde through the circumflex artery. As the artery enters the tunnel, Fig. 15B, there appears to be no narrowing or pinching of the vessel. Fig. 15C shows the artery one quarter of the way along the tunnel, with many branches containing India ink. In the first third of the tunnel the artery breaks up into arteriolar branches and into many almost cavernous-like cavities which contain India ink. In the central portion of the tunnel the vessel divides into two main complexes, Fig. 15E, one of which when followed through the tunnel branches and disappears; the other continues to branch and eventually reconstitutes itself into the artery, Fig. 15F. Perhaps the strangest fact is that the vessel is still open and branching at the very end of the tunnel, Fig. 15G. Even here there is no evidence of intimal proliferation.

Pericardial fat pad graft:

At the time of retrograde circumflex injection, India ink was seen entering the vessels of the diaphragmatic fat pad. This had been grafted to the left ventricular myocardium at the time of operation after careful removal of the epicardium. Microscopic examination of the point of contact between the fat pad graft and the heart muscle is seen in Fig. 16. There is little fibrous reaction at the graft site, and there are many vessels of fair size lying in the fat pad graft which contain India ink which had been injected retrograde through the circumflex artery.

DISCUSSION

The condition of the seven internal mammary arteries examined is shown in Table III. Of the seven vessels only one was thrombosed, i.e. 14.2 per cent and 85.8 per cent remained open. One was examined 18 months after implantation and showed no evidence of intimal proliferation.

Apparently, communications between the implanted vessel and myocardial sinusoid-like spaces are established as early as 82 hours. This is long before actual branching occurs, since we know from animal digestion casts that the artery only starts to bud around the 12th day after implant, and does not form true arteriolar branches before three to four weeks, Further, we know that in the human, as in the animal, the implanted internal mammary artery forms mammary-coronary anastomoses by sending out arteriolar-like branches within the myocardium. These are known to have persisted for 18 months and did not disappear after a few weeks —as has been suggested by Glenn.[15] Certainly, in the patient in whom the artery was left in an ischaemic heart for 18 months, there was no appreciable evidence of the intimal proliferation reported by Bailey, Bakst *et al*, in animals. In fact, the artery remained open for the entire length of the tunnel. This has never occurred in internal mammary artery implants in animals, even in hearts rendered partially ischaemic by anterior descending branch ligation. Usually, the portion of the internal mammary artery distal to the point of branching shows varying degrees of narrowing of the lumen due to intimal proliferation in the animal heart, even though there is little or none proximal to the point of branching within the tunnel.

In our animal studies we have shown that the direction of blood flow through the implanted internal mammary artery is *into the heart* and not from the heart into the internal mammary artery.

In a patient such as the last, who was totally disabled by angina decubitis prior to implant, and in whom pain disappeared and there was marked increase in exercise tolerance, there can be little doubt that his heart received extra-cardiac arterial blood through the patent, branching implanted vessel.

In our series of 54 internal mammary artery implants in human cases of coronary artery insufficiency, 74 per cent were totally disabled by anginal pain and 84 per cent had had one or more known infarctions prior to surgery.

No patient was operated upon as a preventive measure. All except one suffered from anginal pain.

We cannot agree with Beck and Leighninger[16] who state that "any patient in whom the diagnosis of this disease" (coronary artery insufficiency) "is established is a candidate for operation providing the disease has not advanced to a point where risk of operation is too great."

In our series 15 of the group suffered angina decubitus. Of these nine died—a 60 per cent mortality. There were 39 patients with no angina at rest. Of these three died—a 7.6 per cent mortality (Table IV).

Of 49 patients followed six months to 5½ years (Table V), 30 had no angina at rest; 74 per cent of these were totally disabled prior to surgery, and 85.7 per cent became pain-free or had slight pain. There were 14 cases of angina decubitus, 21 per cent of whom became pain-free or had slight pain, and 28 per cent returned to work after internal mammary artery implantation and pericardial fat pad graft.

SUMMARY

Evidence has been presented to show that the internal mammary artery implanted into the human heart that is ischaemic as a result of coronary artery disease, remained open in 85.8 per cent of the seven hearts studied,

Further, in the artery examined 18 months after implantation, not only was the artery open and branching, but it showed little intimal proliferation.

The clinical results in which 75 per cent of patients with coronary artery insufficiency were relieved of anginal pain after internal mammary artery implantation corresponds to the known mammary-coronary anastomotic rate in animals.

The cases mentioned were operated upon at the Royal Victoria Hospital, Montreal Institute of Cardiology, Jewish General Hospital and Queen Mary Veterans Hospital, Montreal, Canada.

RESUMEN

Se presentan evidencias de que la arteria mamaria interna implantada dentro del corazón humano isquémico como resultado de la enfermedad coronaria, permaneció abierta en su luz en el 85.8 por ciento de los siete corazones estudiados. Además, en la arteria examinada 18 meses después de la implantación no sólo estaba permeable y emitiendo ramas, sino que mostró pequeño proliferación de la íntima.

Los resultados clínicos en los que el 75 por ciento de los enfermos con insuficiencia coronaria se aliviaron del dolor anginoso después de la implantación de la arteria mamaria interna, corresponden a la proporción en que se sabe se obtienen la anastomosis mamario-coronaria en los animales.

RESUME

L'auteur démontre que l'artère mammaire interne implantée dans un coeur ischémié par une atteinte coronarienne resta perméable dans 85,8% sur les 7 cas étudiés. De plus, après 18 mois d'implantation, non seulement l'artère était perméable et implantée, mais elle montrait en outre une petite prolifération de l'intima.

Les résultats cliniques, dans lesquels 75% des malades atteints d'insuffisance coronarienne furent soulagés de leurs douleurs angineuses après implantation de l'artère mammaire, correspondent à la proportion connue des résultats de l'anastomose coronarienne-mammaire chez les animaux.

ZUSAMMENFASSUNG

Es wurde Beweismaterial vorgelegt, um zu zeigen, dass die art. mammar. int, wenn sie in das menschliche Herz implantiert wird, das ischaemisch ist infolge Coronar-Arterienerkrankung, in 85,8% der sieben überprüften Herzen offen blieb. Ausserdem waren die 18 Monate nach der Implantation untersuchten Arterien nicht nur durchgängig und verzweigt, sondern zeigten auch nur geringe Intima-Wucherungen.

Die klinischen Ergebnisse, wonach 75% der Patienten mit Coronar-Arterien-Insuffizienz von ihren anginösen Schmerzen befreit wurden nach Implantation der art. mammar, int., entsprechen der bekannten Mammaria-Coronarien-Anastomosenrate bei Tieren.

REFERENCES

1 Vineberg, A. M.: "Development of an Anastomosis between the Coronary Vessels and a Transplanted Internal Mammary Artery," *C.M.A.J.*, 55:117, 1946.

2 Vineberg, A. and Miller, G.: "Internal Mammary-Coronary Anastomosis in the

Surgical Treatment of Coronary Artery Insufficiency," *C.M.A.J.*, 64:204, 1951.

3 Vineberg, A. and Buller, W. C.: "Pericardial Fat Blanket to Supplement Internal Mammary Artery Implant," *C.M.A.J.*, 70:76, 1954.

4 Vineberg, A. M. and Jewett, B. L.: "Development of Anastomosis between Coronary Vessels and Transplanted Internal Mammary Artery," *C.M.A.J.*, 56:609, 1947.

5 Vineberg, A. M. and Niloff, P. H.: "The Value of Surgical Treatment of Coronary Artery Occlusion by Implantation of Internal Mammary Artery into Ventricular Myocardium. Expt. Study," *Surg., Gynec. and Obst.*, 91:551, 1950.

6 Benscome, S. A. and Vineberg, A.: "Histological Studies of the Internal Mammary Artery after Implantation into the Myocardium," *Am. Heart J.*, 45:571, 1953.

7 Vineberg, A. M.: "Development of Anastomosis Between the Coronary Vessels and a Transplanted Internal Mammary Artery," *J. Thoracic Surg.*, 18:839.

8 Vineberg, A. and Miller, D.: "Functional Evaluation of an Internal Mammary Artery Anastomosis," *Am. Heart J.*, 45:873.

9 Vineberg, A., Munro, D. D., Cohen, H. and Buller, W.: "Four Years Clinical Experience with Internal Mammary Artery Implantation in the Treatment of Human Coronary Artery Insufficiency, Including Additional Experimental Studies," *J. Thoracic Surg.*, 29:1, 1955.

10 Bailey, C. P. and Likoff, N. N.: "The Surgical Treatment of Coronary Insufficiency," *Dis. Chest*, 27:477, 1955.

11 Neptune, N. B.: *J. Thoracic Surg.*, 29:1.

12 Bakst, A. A., Maniclia, R., Adam, A. and Bailey, C. P.: "The Physiologic and Pathologic Evaluation of the Implantation of the Internal Mammary Artery into the Left Ventricular Myocardium for the Treatment of Coronary Artery Disease," *Surgery*, 38:49, 1955.

13 Vineberg, A. and Buller, W.: "Technical Factors which Favour Mammary-Coronary Anastomosis," *J. Thoracic Surg.*, 30:411, 1955.

14 Wearn, J. T., Mettier, S. R., Klumpp, T. G. and Zschiesche, L.: "The Nature of the Vascular Communications Between the Coronary Arteries and the Chambers of the Heart," *Am. Heart J.*, 9:143, 1933.

15 Beck, C. S. and Leighninger, D. S.: *J.A.M.A.*, 159:1264.

16 Glenn, F., Hulsnade, G. and Gore, A. L.: *Surgical Forum Clinical Congress of the American College of Surgeons*, 289, 1950.

Pulmonary Arteriovenous Fistulas of the Medial Basal Segment of the Right Lower Lobe: A Note on Absence of Vascular Bruits

ISRAEL STEINBERG, M.D., F.C.C.P.
New York, New York

Classically, pulmonary arteriovenous fistulas are accompanied by vascular bruits. These are located over a segment or lobe of a lung and vary from a faint systolic sound often accentuated by deep inspiration to a loud harsh systolic blow. In a series of 16 cases with pulmonary arteriovenous fistulas studied at The New York Hospital,[1-3] all but two patients (both with fistulas of the medial basal segment of the right lower lobe) had characteristic bruits. The first patient with a pulmonary arteriovenous fistula of the medial basal segment of the right lower lobe, previously reported,[1] and the new case are herein recorded.

Study of the lobar and segmental divisions of the lung reveals that the medial basal segment of the right lower lobe lies deep within the thorax. Indeed, the "cardiac" segment is an alternate term. It is in contact with the heart along its mediastinal border; elsewhere, it is completely surrounded by other segments of the lung. Accordingly, an arteriovenous fistula in the medial segment of the right lower lobe appears to be silent. Because of the absence of a bruit, a high index of suspicion must be maintained. Careful scrutiny of the conventional chest roentgenogram should suggest the possibility of an arteriovenous fistula; angiocardiography will provide the definitive diagnosis.

Case Reports

Case 1: Pulmonary arteriovenous fistula, medial basal segment, right lower lobe, associated with rheumatic heart disease and hypertension. A 72 year old housewife (New York Hosp. No. 319819) was first admitted in 1946 because of blurred vision. A middle fossa meningioma was found, and removal of the tumor resulted in improvement of sight. During her stay evidences of mitral stenosis and insufficiency were elicited. In 1947 she returned because of epigastric cramps. Urologic study at that time disclosed cysts of the right kidney, which were removed. Chest x-ray film (Figure 1A) revealed nodular densities at the right base. The heart was enlarged, especially the right ventricle, pulmonary artery segment and left atrium. The blood pressure in 1946 was normal but in 1947 it had increased to 220/110 mm. Hg.

In 1949 cholelithiasis with obstructive jaundice developed which necessitated cholecystectomy and choledocholithotomy. Auricular flutter appeared prior to operation and was converted by digitalization to fibrillation. The post-operative period was stormy but the patient improved and was discharged. Subsequently she was seen periodically in the out-patient department. Early in 1951 central retinal artery thrombosis developed and she was readmitted to the hospital. This time the roentgen findings at the right base were suspected to be due to a pulmonary arteriovenous fistula; however, no bruit was heard and clubbing, polycythemia, and cyanosis of fingers and toes were not present. Angiocardiography (Figures 1B and C) was performed and an arteriovenous fistula of the medial basal segment of the right lower lobe was demonstrated. There was no history of familial bleeding and telangiectasia.

From the Departments of Radiology and Medicine, The New York Hospital-Cornell Medical Center.

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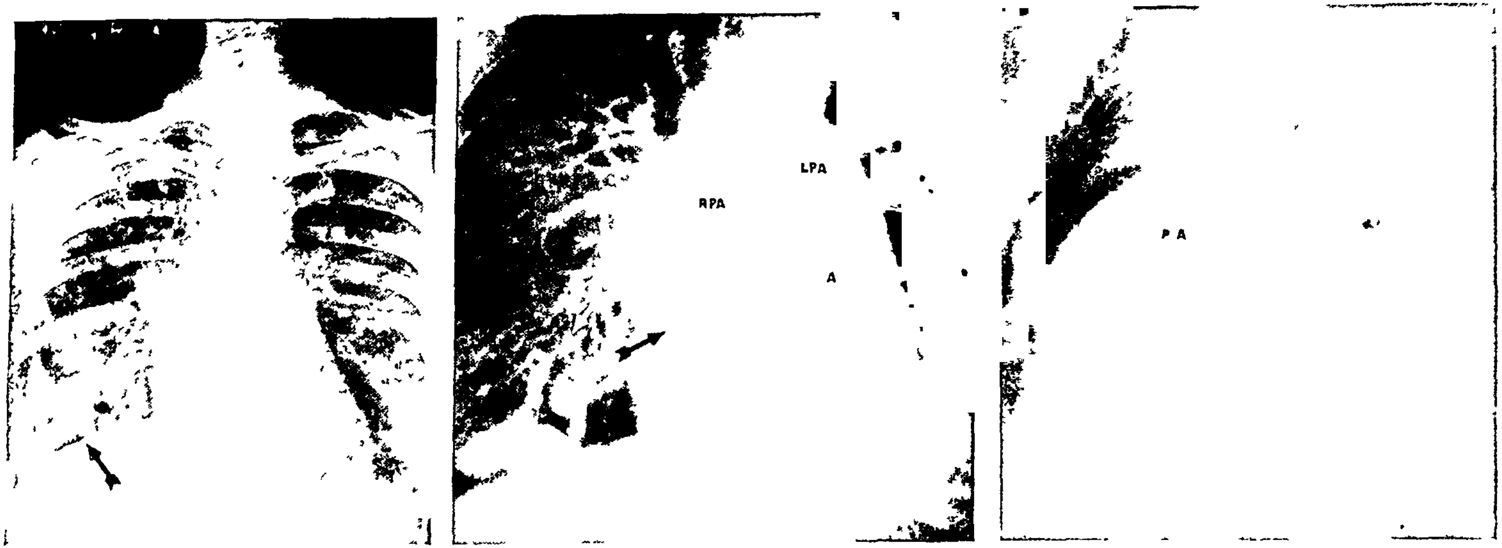

FIGURE 1A FIGURE 1B FIGURE 1C

Figure 1 (Case 1): A. Conventional chest roentgenogram showing a nest of small nodular densities just above the right diaphragm (arrow). The heart, pulmonary artery and branches are enlarged. B. Serial frontal angiocardiogram at five seconds shows a large pulmonary artery (PA) and branches (Right, RPA; left, LPA) due to mitral stenosis. A large segmental pulmonary artery from the right descending branch of the pulmonary artery (white arrow) proceeds to the right lower lobe connecting with a coiled series of rounded densities (arteriovenous fistula) which in turn empty via an efferent vein into the left atrium (black arrow). C. Left lateral angiocardiogram at three seconds shows the opacified main stem pulmonary artery (PA) and branches with an afferent segmental division connecting the circinate arteriovenous fistula of the medial basal segment, right lower lobe. (Republished with permission of Am. J. Med.[1]).

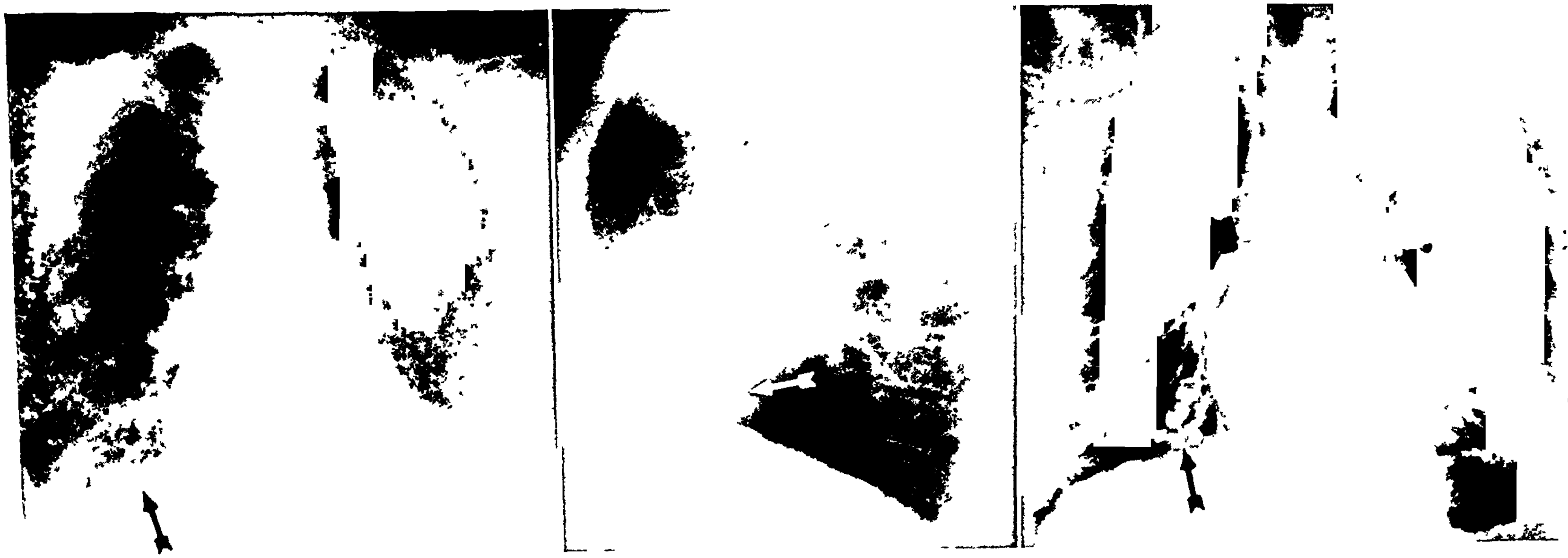

FIGURE 2A FIGURE 2B FIGURE 2C

Figure 2 (Case 2): A. Frontal teleroentgenogram showing a cluster of small rounded densities near the right cardiac border (arrow). B. Lateral x-ray film shows the masses to be located in the medial basal segment of the right lower lobe (arrow). C. Frontal teleoangiocardiogram shows the opacified arteriovenous fistula (arrow).

The electrocardiogram showed right axis deviation, the rhythm varied between auricular flutter and fibrillation. She was last seen on October 17, 1956. She was totally blind and had become disoriented but polycythemia, clubbing and cyanosis of the fingers had not developed. Because of her poor general health and the symptomatic character of the pulmonary arteriovenous fistula, operation was not advised.

Case 2: Asymptomatic pulmonary arteriovenous fistula, medial basal segment of of the right lower lobe. A 64 year old housewife (New York Hosp. No. 684773) was admitted to the hospital for a minor gynecologic operation. A routine chest x-ray film disclosed an abnormal shadow at the right base. She denied respiratory complaints and there was no history of bleeding tendencies in the family. Physical examination revealed a well developed and nourished woman. The chest was clear, bruits were absent. There was no cyanosis or clubbing of the digits and telangiectases of the mucous membranes and skin were absent. The only abnormal findings were elevation of the blood pressure, 180/80 mm. Hg. and left axis deviation of the electrocardiogram. The chest x-ray films (Figures 2A and B) showed clusters of rounded densities with hilar vascular connections located in the medial basal segment of the right lower lobe. Blood studies were normal; the hematocrit was 43 per cent. Angiocardiography was done on August 2, 1956 (Figure 2C) and showed the classical appearance of a pulmonary arteriovenous fistula located in the medial segment of the right lower lobe. She was seen in the out-patient department during the past year. There were no respiratory complaints; however, hypertension persisted. Excision of the pulmonary arteriovenous fistula was advised but refused by the patient.

Comment

Figure 3, modified from Jackson and Huber's[4] and Boyden's[5-7] studies of the pulmonary segments clearly shows the medial basal (cardiac) segment of the right lower lobe to lie well within the thorax. Indeed, it is entirely surrounded by the neighboring segments save along its medial border; here it grooves the heart and is well away from the surface of the thorax (Figure 3B). This apparently explains the inability to elicit a bruit with the stethoscope. Whether a bruit might be heard with electrical magnification has not been ascertained. Since operation was not performed, it was not possible to determine whether a bruit would have been found in the exposed specimen. Boyden[6] rightly takes exception to the omission of a left medial basal segment in the international nomenclature. This segment, too, is adjacent to the heart. Since a pulmonary arteriovenous fistula has not been encountered in this area, it is not known if the bruit will also be absent.

Excision of a pulmonary arteriovenous fistula is recommended even in asymptomatic patients. This is because the incidence of cerebral abscess and thrombosis is high in this disease.[1, 2] In addition, fatal rupture of the paper-thin fistula has also occurred.[8] Even though a retinal thrombosis developed in Case 1, which may be related to the pulmonary arteriovenous fistula, the presence of rheumatic heart disease, hypertension, the advanced age, blindness and finally senility did not warrant operation. However, despite the age, it was recommended for the other patient (Case 2) but she declined surgery.

In both patients the frontal conventional roentgenogram showed a series of nodular densities at the right base adjacent to the right heart border (Figures 1A and 2A). Whether such an arrangement is characteristic of arteriovenous fistulas of the medial basal segment of the right lower lobe is unknown; since only two cases have been studied. Angiocardiography, however, established the diagnosis,[1, 2] despite the absence of a vascular bruit.

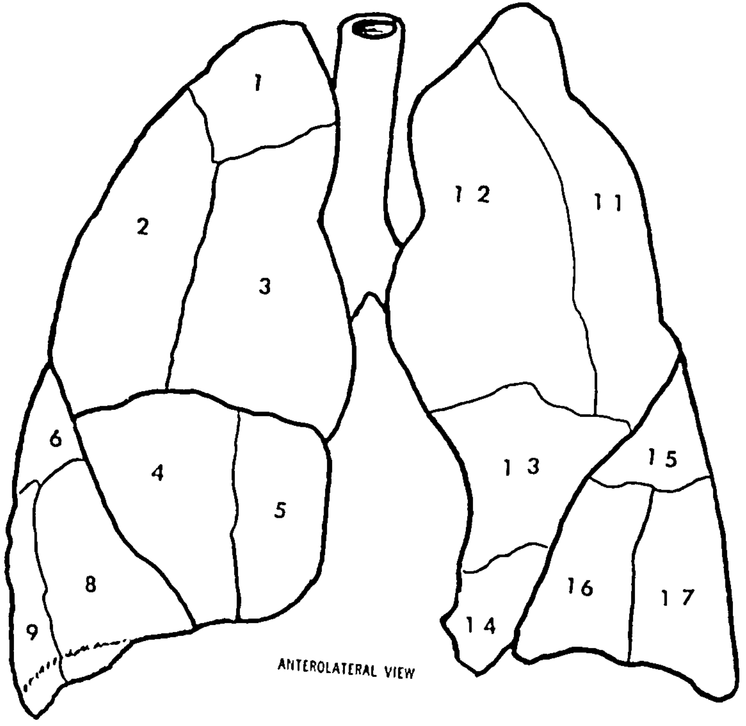

FIGURE 3A

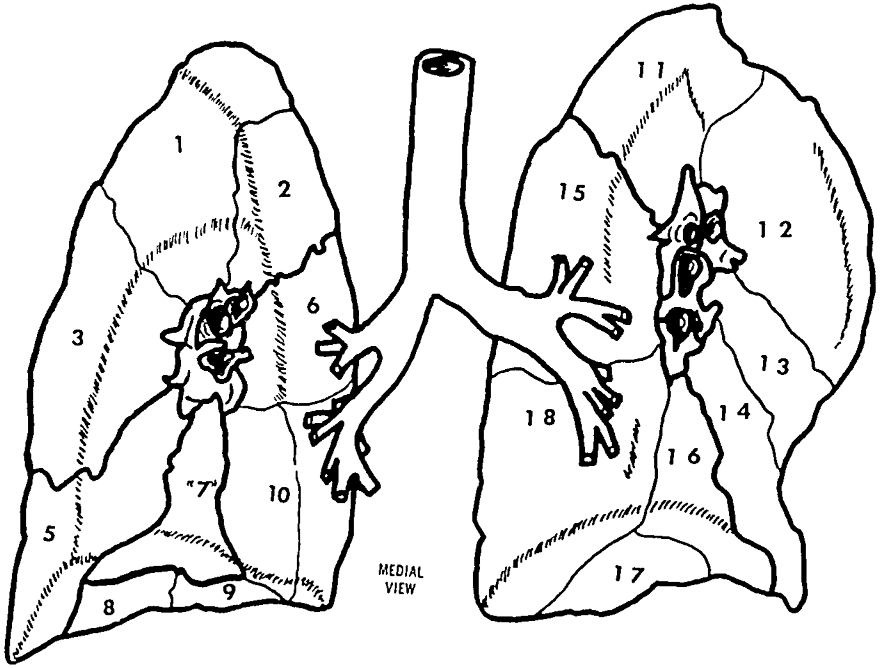

FIGURE 3B

Figure 3: The lobes and bronchopulmonary segments of the lungs. A. Anterolateral view. B. Mediastinal view. (Adapted from Jackson and Huber[4] and Boyden.[5, 6] Note that the medial basal segment of the right lower lobe "7" is located in the mediastinum and does not reach the surface of the chest wall.

Lobes of Left Lung—Upper Division of Upper Lobe: 11. Apical-posterior; 12. Anterior. Lower Division of Upper Lobe: 13. Superior; 14. Inferior. Lower Lobe: 15. Superior; 16. Antero-medial Basal; 17. Lateral Basal; 18. Posterior Basal.

Lobes of Right Lung—Upper Lobe: 1. Apical; 2. Posterior; 3. Anterior. Middle Lobe: 4. Lateral; 5. Medial. Lower Lobe: 6. Superior; 7. Medial Basal; 8. Anterior Basal; 9. Lateral Basal; 10. Posterior Basal.

SUMMARY AND CONCLUSIONS

Two elderly women were discovered, on routine roentgenography of the chest, to have a series of rounded densities with vascular hilar connections located in the medial basal segment of the right lower lobe. Despite the absence of a vascular bruit, angiocardiography was recommended and established the diagnosis of pulmonary arteriovenous fistulas.

Anatomic study of the pulmonary segments discloses that the medial basal (cardiac) segment of the right lower lobe lies deep within the thorax and that disease in this area is inaudible with the stethoscope. A series of rounded densities at the right base that appear to have vascular connections with the right hilus should arouse suspicion of being of vascular origin. Angiocardiography is recommended for diagnosis. If no contraindications exist, surgical excision even in elderly asymptomatic individuals is advised.

Acknowledgment: Thanks are due to Elissa Ettinger for preparation of Figure 3.

RESUMEN Y CONCLUCIONES

Al hacer roentgenfotografía a dos mujeres ancianas se descubrió que tenían una serie de manchas redondas con conexiones hiliares, ubicadas en el segmento medial basal del lóbulo inferior derecho. A pesar de la ausencia de ruido bascular se recomendó la angiocardiografía y se estableció el diagnóstico de fístulas pulmonares arteriovenosas.

El estudio anatómico de los segmentos deja ver que el medial basal (cardiaco) el lóbulo inferior derecho radica muy profundamente en el tórax y que los cambios en esta región son inauscultables con el estetoscopio. Una serie de manchas redondas densas en la base derecha, que parezcan tener anexos vasculares con el hilio derecho deben dspertar la sospcha de ser de origen vascular. Se recomienda la angiocardiografía para el diagnóstico.

Si no hay contraindicaciones la excisión quirúrgica se recomienda aún en personas ancianas asintomáticas.

RESUME

On a découvert à l'examen radiologique systématique du thorax chez deux vieilles femmes une série d'opacités arrondies siégeant dans le segment basal médian du lobe inférieur droit. Malgré l'absence de bruit vasculaire, une angiocardiographie fut conseillée, et elle permit de faire le diagnostic d'anévrysmes artérioveineux pulmonaires.

L'étude anatomique des segments pulmonaires infirme que le segment basal médian (segment cardiaque) du lobe inférieur droit s'étende profondément à l'intérieur du thorax, et qu'une atteinte de cette région soit inaudible au stéthoscope. Un groupe d'opacités arrondies de la base droite, qui semblent avoir des connections vasculaires avec le hile doivent faire soupçonner qu'elles sont d'origine vasculaire. L'angiocardiographie est conseillée pour affirmer le diagnostic. S'il n'existe aucune contre-indication, l'exérèse chirurgicale est recommandée même chez les individus âgés sans symptômes.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Es wurden 2 ältere Frauen bei planmässiger Röntgenuntersuchung des Brustkorbes entdeckt, die eine Reihe von abgerundeten Verdichtungen aufwiesen mit Gefässverbindungen zum Hilus und lokalisiert im medialem besalen Segment des rechten Unterlappens. Trotz des Fehlens von Gefässgeräuschen wurde zur Angiocardiografie geraten, und dies führte zur Feststellung der Diagnose von pulmonalen arteriovenösen Fistelm.

Die anatomische Untersuchung der pulmonalen Segmente enthüllte, dass das Mediale basale (cardiale) Segment des rechten Unterlappens tief im Thorax liegt und dass eine Erkrankung in diesem Bereich mit dem Stetoskop nicht hörbar ist. Eine Reihe von abgerundeten Verdichtungen an der rechten Basis, die Gefässverbindungen mit dem rechten Hilus zu haben scheint, sollte den Verdacht erwecken, vasculären Ursprunges zu sein. Angiocardiografie zur Feststellung der Diagnose empfielt sich, Sofern keine Kontra-Indikationen vorliegen, ist chirurgische Excision selbst bei älteren Symptomenfreien Individuen ratsam.

REFERENCES

1 Steinberg, I. and McClenahan, J.: "Pulmonary Arteriovenous Fistulas: Angiocardiographic Observations in Nine Cases," *Am. J. Med.*, 19:549, 1955.

2 Steinberg, I. and Finby, N.: "Roentgen Manifestations of Pulmonary Arteriovenous Fistulas: Diagnosis and Treatment of Four New Cases," *Am. J. Roentgenol.*, 78:234, 1957.

3 Steinberg, I. and Miscall, L.: "Pulmonary Arteriovenous Fistulas in Mother and Son: Liver Abscess Complications in Mother," *Surg.* (In press)

4 Jackson, C. L. and Huber, J. F.: "Correlated Applied Anatomy of Bronchial Tree and Lung with System of Nomenclature," *Dis. Chest*, 9:319, 1943.

5 Boyden, E. A.: "A Synthesis of the Prevailing Pattern of the Bronchopulmonary Segments in Light of Their Variations," *Dis. Chest*, 15:657, 1949.

6 Boyden, E. A.: "A Critique of the International Nomenclature on Bronchopulmonary Segments," *Dis. Chest*, 23:266, 1953.

7 Boyden, E. A.: *Segmental Anatomy of the Lungs.* McGraw-Hill Book Co., Inc. New York, 1955.

8 Israel, H. L. and Gosfeld, E.: "Fatal Hemoptysis from Pulmonary Arteriovenous Fistula: Report of a Case with Hereditary Telangiectasia," *J.A.M.A.*, 152:40, 1953.

CURRENT THERAPY

With the addition of the Section on Cardiovascular Diseases, we are pleased to introduce a monthly series on current therapy in cardiovascular diseases. This is the first of this series and the Editorial Board invites comment from the readers of our journal.

Digitalis Therapy

Correct digitalis therapy can be considered an art and it has been said that a "life-time of experience" is necessary to master it.[8] Medical students can be taught only the general outlines of digitalis medication; the finer points are acquired only through experience. Certain well established rules exist for the beginning but it is not possible to predict how to proceed or when to stop; every course of digitalis therapy is a new experiment with an unpredictable outcome.

For most patients two or three tablets of 0.1 gm. of the powdered leaf U.S.P. daily will suffice to restore compensation or to slow the ventricles in the presence of atrial fibrillation although in rare instances of advanced heart failure it may be necessary to start with four or five such tablets daily. The end-point is reached when full compensation is restored or when signs of digitalis toxicity develop.

If congestive failure disappears in the course of atrial fibrillation with a rapid ventricular response one usually discontinues larger doses and administers a maintenance dose when the ventricular rate drops to 70 or 80. However, it is often necessary to give much more digitalis as in many cases of this kind the condition of the myocardium requires it.

Even in patients optimally digitalized the liver may remain enlarged, a right sided pleural effusion or ankle edema may persist. Increase in digitalis will not benefit these patients but on the contrary will lead to adverse effects such as general weakness and nausea.

The duration of digitalis therapy is variable. Some patients will require it for a life-time while others with myocardial infarction, pulmonary embolism, streptococcic or viral infections, or active rheumatic fever, may not need any medication once the cause responsible for the failure has disappeared or a strong fibrotic scar developed.

In recent years it has become common practice to replace this classical form of digitalis therapy which requires skill and knowledge by another more mechanical method. Without regard to the patient's age, weight, clinical condition or etiology of the cardiac failure, the "full dose" therapy is applied. The patient receives a calculated "average digitalizing" dose at once or in divided doses within 24 hours, the only disagreement being whether this dose should be 1.2 mg. of digitoxin or more. While the experienced clinician will deliberate whether to increase or decrease the daily dose by one tablet of 0.1 mg. knowing that this may spell the difference between well being and suffering, between digitalization without or with side effects, with or without dangerous arrhythmias, others in the "modern way" try to accomplish digitalization rapidly and with large doses. Actually few patients encountered in hospitals and private practice must be digitalized rapidly. It may be a sign of our times that the quick full digitalization is so widespread and it may also be significant that with this haste the subjective feeling of the patient is often disregarded.

Particularly in elderly patients this method of rapid digitalization often leads to nausea and muscular weakness which may persist for weeks. Even more dangerous and not infrequent is the appearance of dangerous digitalis arrhythmias after as little as 0.6 mg. of digitoxin. On the other hand, some patients will require more than the above doses to obtain maximum benefits. This individualization of digitalis therapy can be compared to that of penicillin therapy for subacute bacterial endocarditis in which we can formulate only general rules at the onset of treatment; we have to modify them according to the clinical and laboratory findings.

Among the side effects the most dangerous are certainly the ventricular tachycardias often leading to ventricular fibrillation. Their danger lies particularly in the fact that they usually do not cause symptoms. They are often preceded by extrasystoles in bigeminal form. It is wrong to speak of them as a sign of digitalis intoxication since they are absent in healthy people even if lethal doses of digitalis are taken. Such extrasystoles appear in the healthy only in the last minutes of life or are completely absent. They appear only terminally in the healthy dog. On the other hand we have seen such extrasystoles particularly in patients with chronic mitral lesions in congestive heart failure even after administration of only 0.3 gm. of standard powdered leaf for one day. Some "abnormal state of the myocardium" is therefore a prerequisite for the appearance of these ectopic rhythms,[7] as we have pointed out for more than 30 years. The nature of this state was unknown until recently. It became clear in the past few years that the appearance of such extrasystoles is favored by a loss of potassium from the myocardial cell.[4] This loss of potassium is known to occur in chronic failure and also during administration of digitalis in large doses. It is impossible to predict when such extrasystoles will occur but they are always threatening. In using the classical method of digitalis therapy one will be able to stop in time when the first extrasystoles appear while with the full dose therapy the single extrasystoles increase in number, characteristic patterns of ventricular tachycardia appear and may be quickly followed by ventricular fibrillation and death. Only careful, continuous supervision and energetic action with the use of potassium chloride orally and quinidine intramuscularly may save some of these patients. When these extrasystoles appear in irregular groups they may on auscultation resemble the rhythm found in atrial fibrillation and therefore more digitalis is given with often fatal results. Digitalis extrasystoles originating in the ventricles show a characteristic continuous change of form. So do ventricular tachycardias. Atrial tachycardias show A-V block.

A-V heart block may also appear after administration of very small doses. Here too the intrinsic condition of the heart is partly responsible.

Ventricular extrasystoles and even ventricular tachycardias not caused by digitalis are no contraindication against the use of the drug. Actually digitalis usually brings about the disappearance of these arrhythmias. Even tachycardia with alternation of the form of the ventricular complexes disappears when digitalis is used.[6]

With regard to the question of rapid digitalization one must admit that most of the time the advantages for the patient are nil and the disadvantages great. Quick digitalization is necessary only under special circumstances: when atrial fibrillation with a fast ventricular rate and low blood pressure or congestive failure is discovered in a patient requiring an emergency operation, when a patient with coronary stenosis develops an atrial paroxysmal tachycardia or atrial fibrillation exists with continuous anginal pain or whether a patient with an acute myocardial infarction develops atrial tachycardia, atrial flutter or fibrillation.

It is known that sublethal doses of digitalis administered to animals cause focal necrosis in the myocardium and certain blood vessels. Such changes have not been reported in man. However, it is probable that although these histological changes that are seen only in severely damaged or dead cells are not demonstrable in man, large doses do lead to some harm to the muscle cells.

At the risk of being repetitious we would like to stress that digitalis therapy in every patient should be regarded as an individual problem. It is impossible to assume that every patient needs the same dose of digitalis for "full digitalization." If one formerly saw too many under-digitalized patients, at present many are over-digitalized and this must be considered a far greater danger. It is one thing to find out statistically what the "average digitalizing" dose is and another to treat every patient with this dose.

Another new aspect of digitalis therapy is the widespread preference for digitoxin. For many physicians it "has become a habit."[5] This is not a new preparation since digitoxin in the form of "digitaline Nativelle" has been isolated and widely used since 1869. Several claims have been made for its recommendation. One is that this preparation does not have to be controlled by bioassay methods. This is true of other isolated glycosides. Moreover, it was found that the potency of several digitoxins available at the present time is not identical; impurities occur which counteract the advantage of giving a "pure" preparation of digitoxin. Another advantage is said to be the complete absorption in the intestinal tract. This would be important if a certain amount of digitalis would always elicit the same response which as we have seen, is certainly not true. Furthermore, because of the different composition and absorption of other preparations of digitalis such as the standardized leaves from the beginning much larger doses are given.

A third claim often made is that digitoxin is a less toxic preparation. This is certainly not correct with regard to nausea, anorexia and even less so with regard to toxic arrhythmias. The claim has also been made that digitoxin acts quicker than other digitalis preparations. This is also not a fact since digitoxin more than the other digitalis glycosides unites with blood proteins and therefore its action on the heart is slower. Preparations from digitalis lanata, such as digilanid C or digoxin work faster and, since their fixation to blood proteins is minimal, they dissipate faster.[1] Digitoxin on the other hand has the advantage of remaining fixed in the heart muscle longer and thus has a more extended action. It will be useful in the many patients needing continuous digitalis action for a prolonged period; however, tablets of standardized leaf contain digitoxin and therefore have the same effect.

It is of interest that digitalis powdered whole leaf tablets are not even stocked by some hospital pharmacies which instead dispense only the isolated glycosides. In one hospital a nurse with five years graduate experience did not know that powdered whole leaf tablets existed.

When quick action is needed such as during a paroxysmal tachycardia an intravenous injection of digilanid C, digoxin or strophanthin is useful. There is no point in injecting digitoxin in emergencies. The binding of the former substances to albumin in the blood being minimal they are of greater benefit to those patients who need only temporary digitalization or who because of the former appearance of extrasystoles require a drug which is more rapidly dissipated.

The statement has been made that digitalis must be given in larger doses when the heart is larger. This is not in accord with our experience and the largest hearts in valvular lesions, as seen in the combination of mitral and aortic lesions with a tricuspid insufficiency need often very small doses of digitalis for maintenance of full compensation. Patients with coronary sclerosis and heart failure need larger doses even if the heart is scarcely enlarged.

It seems that with rapid digitalization and too rapid diuresis thromboembolic phenomena occur more often than when one proceeds in a conservative manner.[3] The weight of the patient should be considered when the dosage of digitalis is evaluated. An analysis and explanation of this and other observations mentioned below will not be possible as long as we do not know how digitalis acts, whether on the muscle proteins or on the enzymes, whether it accelerates dephosphorilization or acts on adenosine triphosphate.

It is well known that under certain conditions digitalis does not improve the failing heart. A typical and unfortunately common example of this observation is cardiac failure in patients with active rheumatic carditis where sometimes cortisone brings about quicker improvement than digitalis does. If one finds in patients with atrial fibrillation that the ventricular rate remains rapid in spite of administration of large doses of digitalis it will often be observed that one of the following situations prevails. A widespread active carditis in rheumatic valvular lesions may be present without other clinical manifestations, particularly, with a normal sedimentation rate. Another condition that may be present is a pulmonary embolism which for unknown reasons makes it impossible to slow the ventricles in the presence of atrial fibrillation. A third condition is masked hyperthyroidism which responds quickly to specific treatment. It should be emphasized here that in many forms of sinus tachycardia digitalis does not slow the heart rate. Even with atrial fibrillation, instances are known where the ventricular rate remained unchanged after administration of 2 mgm. of digitoxin within 24 hours.

During digitalis therapy diuretics are often given and their use may lead to the phenomenon of re-digitalization. The most common effect of this is the appearance of extrasystoles often in form of coupled beats for a few days following a profuse diuresis due to a mercurial diuretic. This effect was originally attributed to the absorption and re-circulation of digitalis from the edematous fluids and the transudates. These fluids were supposed to contain relatively large amounts of digitalis. More recently this has been denied and it has been claimed that the loss of potassium through profuse diuresis is the cause of the extrasystoles. This may well be true but we cannot accept it as the exclusive explanation since louder and more forceful heart sounds or the disappearance of a gallop rhythm indicate improvement in the state of the myocardium. As long as this cannot also be attributed to loss of potassium we will keep the old explanation in mind.

Strophanthin therapy is used too seldom. Many reject it without ever having tried it, while others have thought it useless or weak. It must be remembered that strophanthin although kept under sterile condition will deteriorate rapidly if the glass container or ampoule does not meet certain specifications concerning its content of potassium. Still others do not use it because they observed fatal accidents shortly after the injection. In such cases inquiry will reveal that the dose given was 0.5 mg. which is unfortunately still recommended widely in books and articles. Actually the single dose should rarely exceed 0.25 mg. and should be even less in the patient who has had digitalis in recent weeks or who has responded to former attempts at digitalization with the appearance of extrasystoles. An increasing number of extrasystoles and ventricular fibrillation are the only real dangers of strophanthin therapy and this danger can be avoided with the use of smaller doses and observation of the patient for 30 minutes following each injection. If no extrasystoles appear the dose can be repeated safely the next day. The slowing action on the ventricle in the course of atrial fibrillation is not as pronounced as with digitalis. There is no doubt, however, that preparations such as ouabaine and strophosid do work quicker and often with much less side-effects in patients with myocardial fibrosis, myocardial infarction and heart failure than any other preparation. Strophanthin is dissipated quickly and the injection must be repeated every 24 to 48 hours. The disadvantage of chronic therapy is the necessity for an intravenous injection, since oral or rectal administrations are, for all practical purposes, ineffective; for initiation of a digitalis effect however strophanthin is unsurpassed if speed is essential. It is often dogmatically stated that three days should elapse between the administration of the last dose of digitalis and the first dose of strophanthin. The duration of this interval depends on many factors among which is the response of the patient to digitalis and the type of digitalis used, i.e., whether a long acting cumulative digitalis preparation such as digitoxin or a rapidly dissipated one like digoxin has been given. The use of the recently introduced actyl strophantidine is not without risk because of its fast action.

In recent years gitalin preparations have again been recommended. We used them 30 years ago as Verodigen and found them to be reliable, effective preparations particularly in the form of suppositories. In general there is no remarkable advantage derived from the use of this preparation and the statement is still correct that it does not matter much which type of digitalis preparation is used but how it is used.

DAVID SCHERF, M.D., F.C.C.P.*
NEW YORK, NEW YORK

REFERENCES

1 Eichna, L. W. and Taube, H.: "A Comparison of the Actions of Four Cardiac Glycosides on a Patient with Congestive Heart Failure," *Am. Heart J.*, 26:631, 1943.

2 Fremont, R. E. and King, H.: "Digitoxin Causing Ventricular Tachycardia with Peripheral Vascular Collapse: Report of an Unusual Case," *J.A.M.A.*, 143:1052, 1950.

3 Gormsen, J.: "Does Rapid Dehydration in Cardiac Decompensation Produce Thromboembolic Complications?" *Acta Med. Scand.*, 148:61, 1954.

4 Lown, B., Salzberg, H., Enselberg, C. D. and Weston, R. E.: "Interrelation Between Potassium Metabolism and Digitalis Toxicity in Heart Failure," *Proc. Soc. Exper. Biol., Med.*, 76:797, 1951.

5 Marriott, H. J. L.: "The Ascendancy of Digitoxin and Renaissance of Gitalin," *Ann. Int. Med.*, 40:820, 1954.

6 Scherf, D. and Kisch, F.: "Ventricular Tachycardia with Varyform Ventricular Complexes," *Bull. N. Y. Med. Coll.*, 2:73, 1939.

7 Scherf, D. and Schott, A.: *Extrasystoles and Allied Arrhythmias*, Grune and Stratton: New York, 1953.

8 Wenckebach, K. F.: "The Use of Foxglove at the Bedside," *Brit. Med. J.*, 1:181, 1930.

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*Department of Medicine, New York Medical College.

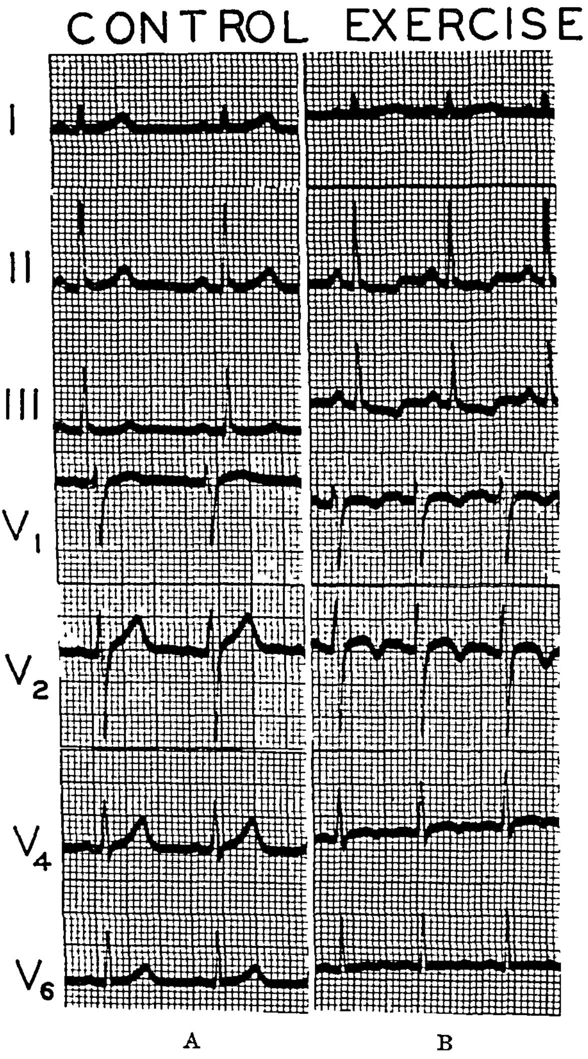
THE ELECTROCARDIOGRAM OF THE MONTH

This "Electrocardiogram Of The Month" is the beginning of a series. The authors would be pleased to receive comment and controversy from readers in relation to explanations offered.

Electrocardiograms A and B were made, respectively, before and after exercise employing a bicycle exerciser. The 26 year old subject has no symptoms and no signs of heart disease. His blood pressure is 120/80. There are no evidences of arteriosclerosis in the peripheral vessels or the eyegrounds. He is not a diabetic. He is apparently in good health.

Explanation

The subject is a healthy intern at the Touro Infirmary who was used as a subject for a controlled study of the effect of exercise upon the electrocardiogram.



The inversion of the T waves in Lead II and III and in the precordial leads is commonly observed with rapid rate, after 20 rapid deep knee bends, or after a period of bicycle exercise sufficient to cause dyspnea. The inversion of the T waves in the middle and right precordial leads is more unusual as a purely exercise effect. However, it is commonly observed after hyperpnea and in this instance it is also due to the fact that the mean T effects are made to point upward (away from all of the chest electrodes) when the exercise causes a marked diminution in the magnitude of the ventricular gradient.

Less exertion produces similar effects if performed 30 minutes to an hour after a meal. Smoking has a marked effect in some persons. Many errors in diagnosis result from the prevalent deep-rooted prejudice against inverted T waves in lead II and in the left precordial leads. These are commonly interpreted as abnormal regardless of the circumstances under which they are observed. It seems clear to us that in many instances the proper evaluation of low or inverted T waves can only be made by studying tracings made 1) under basal conditions, 2) after exercise, 3) after a meal, 4) after exercise performed 45 minutes following a meal. The series of observations should be made on the same morning. In some cases the effects of other factors should be observed (e. g., smoking).

MANUEL GARDBERG, M.D.
IRVING L. ROSEN, M.D.
NEW ORLEANS, LOUISIANA
Cardiac Research Laboratory, Touro Infirmary and the Department of Medicine, Louisiana State University Medical School.

Carcinoma in Collagen Disease

With an Illustrative Case Report

B. GOLBERG, M.B., and P. E. BALDRY, M.B.

London, England

The association of carcinomatous changes with lupus erythematosus of the skin has been recognised since 1886, when the first cases were described by Riessmeyer and also by Curie. In 1934 Uhlmann and Schambye[1] were able to collect 107 cases from the literature. Kappesser[2] analysed 140 cases in 1952 and calculated a maximal incidence of carcinomatous change of one in every 52 cases of lupus erythematosus of the skin. He found 81 of 87 of the tumours to be squamous cell carcinomas, four were basal-cell carcinomas and two were mixed-cell types. Schwarz[3] (1953) found the incidence in the patients attending his clinic to be one in 213. Köpf[4] demonstrated the first spindle-celled fibrosarcoma in such skin lesions in 1946 and Grasreiner and Sterba[5] published a further spindle-celled fibrosarcoma in 1954. Tar carcinoma of a lupus erythematosus scar has been described by Rosmanith.[6]

Whether a specific etiologic relationship exists between these skin lesions and the malignant changes is controversial. Schwarz[3] has outlined three possibilities: (a) the conjunction of the two conditions may be accidental; (b) the treatment of the lupus lesions by irritants such as caustics or irradiation, promotes the development of malignant change; (c) there is a specific predisposition to malignant change in the skin lesions of lupus erythematosus. In his series 10 per cent were previously untreated, and he concluded that the predisposition was not specific, but similar to that found with lupus vulgaris, burn scars, radiation damage, chronic light sensitivity, and other conditions in which skin atrophy occurs. In Montgomery's[7] experience there was a lower incidence of epitheliomatous change in lupus erythematosus than in lupus vulgaris.

Whatever the ultimate conclusion about this relationship, there is no doubt that carcinomatous change is frequent in lupus erythematosus of the skin. We have not, however, been able to find a reference in any of the major publications on the subject to carcinomatous change occurring in other organs affected by the visceral changes of systemic lupus erythematosus.

The association of malignant disease with other collagen diseases has been repeatedly noted in dermatomyositis. The first description of visceral changes in this disease by Urbach[8] in 1930 was soon followed by Bezecny's[9] report of three cases with associated carcinoma of the ovary or breast.

From the Ashford Chest Clinic, Ashford, Middlesex, England.

Sheard and Knoepfler[10] were able to collect 70 cases associated with malignant disease by 1956, the predominant site of the malignant change being in the gastro-intestinal or genital tract. Cases associated with carcinoma of the lung have been frequently described.[11-14] Schuermann[15] contrasted the situation with that in scleroderma, also a collagen disease, and one sometimes difficult to differentiate from dermatomyositis. In his study of 600 cases of scleroderma over 20 years he failed to find a single instance of associated malignancy. Zatuchni et al[16] were to describe the first such cases in 1953. In each of their three cases an unsuspected terminal bronchiolar ("Alveolar-cell") carcinoma was found in association with the pulmonary fibrosis of scleroderma. In addition they reported three other malignant lesions in a series of 39 patients with scleroderma, two being carcinomas of the breast in women and one an undifferentiated widely disseminated fibrosarcoma in a man. Jonsson and Houser[17] have since added a case of bronchogenic adenocarcinoma in a woman with scleroderma. Carcinoma of the lung has also been described in conjunction with widely ranging conditions apart from the collagen diseases, and in asbestosis an etiologic relationship is believed to exist.

The close association between dermatomyositis and visceral tumours has given rise to several etiological conceptions. Brunner and Lobraico[18] and Curtis et al[19] have suggested that the cutaneous lesions are the result of sensitisation to the products of the tumour or its destruction. Becker et al[20] postulate a minimal metastic infiltration of skin and muscle, with a resulting inflammatory mesenchymal reaction and destruction of the neoplastic cells. Various authors have reported amelioration of symptoms of dermatomyositis coincidental with effective treatment of the malignant tumour.[19, 20] Bezecny[9] reported improvement in skin and muscle manifestations after excision of the primary tumour in three cases, to be followed in one by recurrence at the appearance of metastases. Similar experiences have been reported by Dostrovsky et al.[11]

Carcinoma of the lung is the commonest of all neoplasms to give rise to remote manifestations not due to obvious metastases. Syndromes suggestive of rheumatoid disease have been described, with joint pains and the development of chronic arthritis sometimes leading to the complete picture of hypertrophic pulmonary osteoarthropathy. In addition neurological disturbances have recently been reported which include primary sensory neuropathy, mixed motor and sensory polyneuritis, acute cortical cerebellar degeneration and various myopathies such as are found with dermatomyositis. These various complications often precede other signs of the tumour by long intervals. Curtis et al[19] in eight cases of dermatomyositis, found the latent period to be on an average of 18.6 months. Miller[21] in a review of the subject, discusses some of the possible ways in which such complications could arise, concluding that they may represent a sensitisation reaction to some antigenic product of the growth. In serum sickness, a frankly allergic disorder, radicular and peripheral neuropathies are well known.

There is thus mounting evidence that a variety of conditions ranging from dermatomyositis to peripheral neuritis and myopathies can be associated with carcinoma of the lung. These manifestations frequently precede the clinical appearance of the neoplasm, and generally improve if not disappear, with its successful extirpation. It seems likely that in such cases the relationship is an etiological one, and that some product of the tumour is the intermediary, effective either directly on the tissue involved, or acting through a process of sensitisation.

We here present a case in which systemic lupus erythematosus was found associated with an oat cell bronchial carcinoma. These conditions have not, apparently, been previously described together, and their possible relationship is discussed.

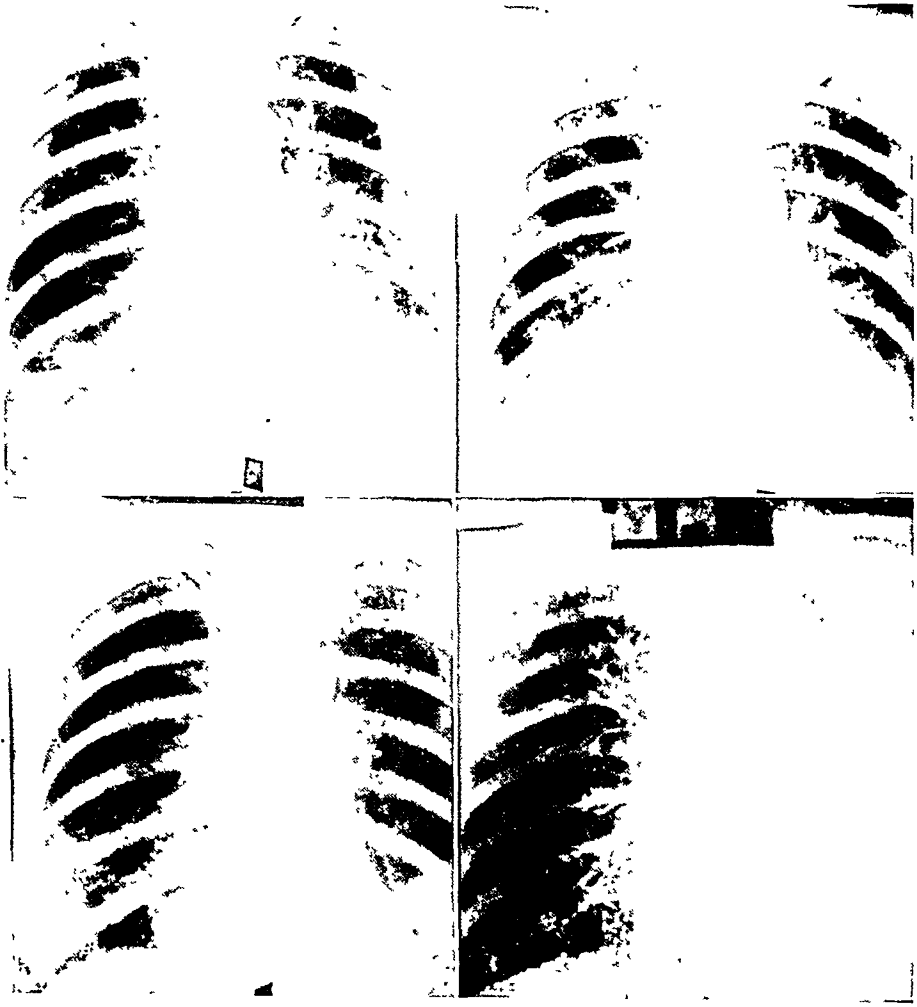


FIG. 1

FIG. 2

FIG. 3

FIG 4

Figure 1: Hospital admission film showing small area of mottling left midzone.—*Figure 2:* Some collapse of right middle and lower lobes, and also left lower lobe. Pleural changes present.—*Figure 3:* Right lung clear. Tight collapse of left lower lobe (due to carcinoma) concealed behind heart shadow.—*Figure 4:* Bronchogram showing collapse of whole left lung, with almost complete obstruction of left main bronchus.

Case Report

A woman aged 49 first attended as an outpatient in January 1955 with a history of a persistent cough, wheezing and a small amount of sputum for many years. On three occasions, towards the end of 1954, there had been small amounts of blood in the sputum at the time of severe bouts of coughing.

She had had a mild attack of rheumatic fever at 17 years of age and two episodes of left-sided pleurisy in 1930 with "congestion of the lung" in 1935. She had smoked 20 to 30 cigarettes a day all her adult life.

On examination there was no abnormal physical sign and a chest radiograph showed the lungs to be clear. As she had been working in a factory for the previous 10 weeks where much ammonia was used, her symptoms were attributed to the aggravation of a long-standing bronchitis by the ammonia fumes.

After giving up this work she remained well until April 1955, when she suddenly became extremely ill, with a high fever, dyspnoea and blood-stained sputum. On admission to hospital generalised rhonchi and rales were heard anteriorly in the left upper and mid-zones of the chest. The initial chest radiograph (Figure 1) showed only a small area of mottling in the left mid-zone, which did not seem sufficient to account for the severity of her condition, but Haemophilus influenzae and Staphylococcus aureus were grown from the sputum. White cell counts ranged between 5,500 and 6,300 per cubic mm. with about 70 per cent neutrophils. Treatment, first with penicillin (½ a mega. unit twice daily for four days) and then tetracyclin (250 milligrammes every six hours for four days) had no effect on her condition, and during this time physical signs of collapse and consolidation of the right lower lobe appeared. This was confirmed by further radiographs (Figure 2) which also showed some collapse to be present in the left lower zone. Chloromycetin (500 milligrammes every six hours) was then given and with this the infection was brought under control. During this time a soft apical systolic murmur was occasionally heard. She was discharged May 12, 1955 and when seen as an outpatient May 24, 1955 was symptom free. A radiograph showed the right side to have cleared completely, but there was still a slight amount of inflammatory change in the left lower zone.

She remained well until the beginning of July, when a butterfly erythematous rash developed over her nose and cheeks, with the typical appearance of lupus erythematosus. The rash extended around her mouth, down her neck and affected her hands. About this time cough with a slightly blood-stained sputum returned. She also complained of pain and swelling of the left knee, and marked tenderness over the anterior ends of her ribs. She was readmitted to the hospital July 20, 1955. In addition to the rash and joint changes there were now physical signs of a collapse of the left lower lobe, confirmed by a radiograph (Figure 3). The soft apical systolic murmur heard previously reappeared. Albumin and a moderate number of red blood cells were found in the urine. Blood examination showed a leucopenia (4,650 white cells per cmm. with 60 per cent neutrophils). A diagnosis of acute systemic lupus erythematosus was made, although bone marrow examination on two occasions failed to show the presence of L. E. cells. Treatment with ACTH (80 milligrammes a day) was started and resulted in marked improvement in the rash and joint pains. At this time it was considered that the lesion in the left lung was due to lupus erythematosus and it was hoped to confirm this by histological examination of a bronchoscopic biopsy. This investigation had to be postponed however, because the rash had extended around her mouth and made her lips inflamed and tender. While waiting for this to improve, bronchography was carried out and showed that the collapse had now involved the whole of the left lung, the left main bronchus being completely occluded (Figure 4). Bronchoscopy at this stage showed the lumen of the left main bronchus, just below the carina, to be obstructed by granular swelling. A biopsy showed the histological appearances of oat cell carcinoma.

Her general condition precluded any surgical treatment, there being evidence of renal involvement with urinary symptoms and red blood cells in her urine. ACTH was continued and seemed to keep the lupus erythematosus under control. The rash remained much less marked and although red blood cells persisted in her urine, a blood urea estimation towards the end of the illness was within normal limits (24 milligrammes per 100 milliliters). Nevertheless she gradually became weaker and died December 1, 1955. Post-mortem examination was refused.

Discussion

Although the diagnosis of systemic lupus erythematosus could not be confirmed by the finding of L. E. cells in this case, many of the characteristic features of the disease were present. At least eight of the 10 criteria laid down by Jessar et al[22] were fulfilled. The butterfly rash, acute migratory polyarthritis, changing cardiac murmurs, varying overt and microscopic haematuria, albuminuria, pulmonary signs apart from those attributable to the carcinoma, anaemia, and persistent leucopenia despite acute pulmonary infection, all indicated a severe systemic disorder clinically in keeping with systemic lupus erythematosus. The response to ACTH with recrudescence of rash and polyarthritis when dosage was reduced was also in favour of this diagnosis.

During the patient's two hospital admissions the pulmonary manifestations of left-sided pneumonia followed by right-sided lower lobe collapse, which both cleared, only to be succeeded at an interval by left lower lobe collapse, are in keeping with the description by Gould and Davies[23] of the radiological findings in their large series. Harvey et al[24] in a clinical analysis of 138 cases found pleural involvement one of the hallmarks of systemic lupus erythematosus and also described persistent pulmonary consolidations lasting up to eight months, with chronic interstitial pneumonitis leading to atelectasis and respiratory failure. Lung changes were found in 46 of 105 patients. Twenty had changes considered to be produced by the lupus, six had pulmonary tuberculosis, five lobar pneumonia, two lung abscess, nine lobular pneumonia, two aspiration pneumonia and one repeated haemoptyses. The last is of interest in view of the presenting symptoms in our case.

In retrospect it seems likely that these presenting symptoms, of cough and haemoptysis, were due to the carcinoma of the left main bronchus, which had not reached a size sufficient to produce radiological abnormality. The distinctive features of the lupus subsequently masked those of the neoplasm. Similar problems arose in the case reported by Williams and Lundberg,[25] where there was the association of systemic lupus erythematosus, a meningioma and carcinoma of the cervix. Here the neurological signs and symptoms, at first attributed to the lupus, only cleared after the diagnosis and successful removal of the meningioma.

It is tempting in our case to relate the lupus to the carcinoma, and postulate that, as in skin lupus, the lesions in the bronchial mucosa were potentially malignant, the carcinoma being precipitated by the irritant effects of heavy smoking and later exposure to ammonia fumes; or to suggest that a primary bronchial neoplasm gave rise to the clinical picture of systemic lupus erythematosus through some mechanism of tissue sensitisation. In the case described by Jonsson and Houser,[17] in which there was a 10 year history of scleroderma, the diffuse interstitial lung fibrosis was thought to be the likely cause of the carcinoma. In ours the relationship may have been accidental, and this is supported by the fact that no other case has apparently been previously described. However, the association of scleroderma with malignant disease had not been found, although sought for, until 1953,[16] since when seven cases have been reported. It may be that carcinoma will prove to be as frequent an occurrence in lupus erythematosus as in other collagen diseases.

REFERENCES

1 Uhlmann, E. and Schambye, G.: "Lupus erythematosus und carcinom," *Arch. f. Dermat. u. Syph.*, 170:500, 1934.

2 Kappesser, R.: "Uber die Entwicklung Karzinomatoser Veränderung auf Erythematodesherden," *Zschr. Haut u Geschlkr.*, 12:11, 1952.

3 Schwarz, J.: "Carcinomenstehung im lupus erythematodes chronicum," *Zschr. Haut u Geschlkr.*, 14:6, 1953.

4 Köpf, O.: "Sarcoma in erythematode," *Hautarzt.*, 5:1, 1954.

5 Grasreiner, W. and Sterba, R.: "Uber Sarkoma in erythematode," *Zschr. Haut u Geschlkr.*, 17:10, 304, 1954.

6 Rosmanith, J.: "A Case of Tar Carcinoma of the Scar Following Lupus Erythematosus," *Pracovni lek (arstvi)*, 5:5, 1953.

7 Montgomery, H.: "The Pathology of Lupus Erythematosus," *J. Invest. Dermat.*, 2:343, 1939.

8 Urbach, E.: "Dermatomyositis Pseudoleucaemica," *Arch. f. Dermat. u Syph.*, 162: 27, 1930.

9 Bezecny, R.: "Dermatomyositis," *Arch. f. Dermat. u Syph.*, 171:385, 1935.

10 Sheard, C. and Knoepfler, P. T.: "Dermatomyositis and the Incidence of Associated Malignancy," *Connecticut M. J.*, 20:8, 1956.

11 Dostrovsky, A. and Sagher, F.: "Dermatomyositis and Malignant Tumour," *Brit. J. Dermat.*, 58:52, 1946.

12 McCombs, R. P. and MacMahon, H. E.: "Dermatomyositis Associated with Metastasising Bronchogenic Carcinoma; Clinico-Pathological Conference," *M. Clin. North America*, 31:1148, 1947.

13 Quiroga, M. I. and Böttrich, H.: "Dermatomiositis y cáncer visceral," *Prensa méd. argent.*, 36:2107, 1949.

14 Bouton, J., Mendoza, D. and Ravera, J. J.: "Dermatomiositis y cáncer pulmonar," *El Tórax (Montevideo)*, 2:4, 1953.

15 Schuermann, H.: "Nachtrag zur malignes Tumore bei Dermatomyositis und progressiver Sklerodermie," *Arch. Dermat. u. Syph.*, 193:628, 1952.

16 Zatuchni, J., Campbell, W. N. and Zarafonetis, C. J. D.: "Pulmonary Fibrosis and Terminal Bronchiolar, ('Alveolar-Cell') Carcinoma in Scleroderma," *Cancer*, 6:6, 1953.

17 Jonsson, S. M. and Houser, J. M.: "Scleroderma (Progressive Systemic Sclerosis) Associated with Cancer of the Lung," *New England J. Med.*, 255:9, 1956.

18 Brunner, M. J. and Lobraico, R. V., Jr.: "Dermatomyositis as Index of Malignant Neoplasm," *Ann. Int. Med.*, 34:1269, 1951.

19 Curtis, A. C., Blaylock, H. C. and Harrell, E. R., Jr.: "Malignant Lesions Associated with Dermatomyositis," *J.A.M.A.*, 150:844, 1952.

20 Becker, S. W., Kahn, D. and Rothman, S.: "Cutaneous Manifestations of Internal Malignant Tumours," *Arch. Dermat. and Syph.*, 45:1069, 1942.

21 Miller, H.: "Neurological Complications of Carcinoma," *Progress in Clinical Medicine*, p. 298. J. & A. Churchill Ltd., London, 1956.

22 Jessar, R. A., Lamont-Havers, R. W. and Ragan, C.: "Natural History of Lupus Erythematosus Disseminatus," *Ann. Int. Med.*, 38:717, 1953.

23 Gould, D. M. and Davies, M. L.: "Roentgenologic Findings in Systemic Lupus Erythematosus," *J. Chronic. Dis.*, 2:2, 1955.

24 Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L. and Schoenrich, E. H.: "Systemic Lupus Erythematosus," *Medicine*, 33:4, 1954.

25 Williams H. M. and Lundberg, G. A., Jr.: "Systemic Lupus Erythematosus, Meningioma, and Carcinoma of the Cervix," *Connecticut M. J.*, 20:8, 1956.

Editorial

The Contribution of the International Congresses on Diseases of the Chest to International Understanding

Walter Pater wrote that a concentration of interest is precedent to the finest flowering of the arts, sciences, philosophies, and life itself. This explains the basis of the great contribution to international understanding and friendship made by Congresses of the American College of Chest Physicians; they are built around a concentration of interest—specialism in diseases of the heart and lungs.

Specialisms in crafts and professions are the hallmark of a highly-developed and integrated community. They are not something new. Herodotus described them in Egyptian medicine of 4,500 years ago. For their beginnings there are two outstanding reasons: Public demand, to fulfill a social need of the times, and the inherent desire in some men to do one or two things efficiently rather than many things adequately. For their growth to fruition on correct lines one thing is especially necessary: An interchange of viewpoints in frank discussion.

The field of research has made such enormous advances in theory, technique and apparatus that it is now beyond the scope of one man to attain full efficiency in more than one branch of medicine. Moreover it is rare for one opinion to be enough; the specialist in diseases of the chest requires the support and checking of one or more scientific investigators, with their laboratory tests, radiography and electrical readings, and often such collaborators must be called in at regular intervals in order to assess the value of treatment or the prognosis of the illness. That is why the College embraces so many allied specialisms.

The chest specialist cannot afford to let up on his reading if he is to retain his own self-respect, and to have the highest of all prizes in the respect of his colleagues. He must know what his fellow-specialists are doing in countries outside his own; better still he must try to meet them, know them, and correspond with them.

International conferences help us to acquire the art as well as the science of our specialism; listening to learned papers is not the whole story. Graphs and statistics can give broad indications on treatments and their results, but patients often beat mathematical prognosis and refuse to fall into neat categories. The real value of our conferences comes out in panel discussions, and in those intimate sharings of experience that result from the social programmes, when we "talk shop." It is then we learn that the personal factors that explain reactions to illness are universal; that in dealing with our own patients we are dealing with citizens of the world.

Above all, we make lasting friendships. Every International Congress results in growing correspondence with fellow-members, from Athens to Oslo, Johannesburg to New York, Taiwan to London. A member of the College is not an Indian or a Californian or a Scotsman; he is a colleague in a medical fellowship. To meet him anywhere is to meet a friend; to be at war with him is unthinkable.

RICHARD R. TRAIL, M.D., F.C.C.P.*
LONDON, ENGLAND

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*Regent for England.

The President's Page

A New Year has just begun and there are many College activities to which we may look forward—the 24th Annual Meeting to be held in San Francisco this spring, the Fifth International Congress in Tokyo, September 7-11, and many chapter and regional meetings.

The Interim Session of the College held in Philadelphia last month, was a tremendous success. The Scientific Program, prepared under the chairmanship of Dr. Robert V. Cohen, drew a record attendance of over four hundred members and guests. I would like to congratulate Dr. Cohen and his committee on the fine program, and thank the officers and members of the Pennsylvania Chapter of the College for their splendid hospitality.

Plans for our Annual Meeting and for our next International Congress are progressing satisfactorily, and I trust that many of the members of the College are planning to attend these two important sessions.

I would like to make a *very important* announcement regarding the 24th Annual Meeting of the College to be held at the Fairmont Hotel in San Francisco, June 18-22. Most of you are aware of the acute hotel situation in San Francisco, and *in order to be assured of satisfactory hotel accommodations during our Annual meeting,* it is essential that you follow the proper procedure. If you are planning to attend the College meeting *only,* and not stay over in San Francisco for the Meeting of the American Medical Association, complete the coupon on page xxiii, and send it *at once* to the San Francisco Convention and Tourist Bureau, via air mail, with the required deposit. If you plan to remain in San Francisco for all or a portion of the American Medical Association meeting June 23-27, *it is essential* that you attach to the College coupon a completed hotel reservation form clipped from an issue of the Journal of the American Medical Association. Applications for reservations will be accepted by the Convention Bureau in the order in which they are received and only by following this procedure can you be assured of remaining in the same hotel for both the College and the American Medical Association meetings. I have been informed that the first hotel reservation coupon will appear in the January 4th issue of the *Journal of the American Medical Association,* and I cannot stress too strongly the importance of sending in the coupons at once. Unfortunately San Francisco does not have a sufficient number of rooms in the larger hotels to accommodate every physician who plans to attend the meetings. There are, however, many excellent accommodations in the smaller hotels and the new tourist courts are recommended by the Convention Bureau.

The Board of Regents of the College adopted a resolution at the Interim Session in Philadelphia to expand the College committees so that our members in all countries will have an opportunity to participate in committee activities. The international committees will meet at the time of our international congresses to discuss their programs and present reports. Plans are now being put into effect to organize these committees so they will be able to meet in Tokyo.

The Board of Regents accepted an invitation from the Honorable Edwin L. Mechem, Governor of the State of New Mexico, to hold a homecoming meeting of the College in his state in 1959. During that year the College will celebrate its Silver Anniversary and a number of special events will be arranged. The College held its first meeting in Albuquerque in 1935 and it is appropriate that we return to celebrate our Twenty-Fifth Anniversary. The City of Albuquerque has pledged its support to the College in this homecoming celebration. The meeting in Albuquerque is planned for the fall and will be held in addition to the 25th Annual Meeting of the College scheduled for June 3-7, 1959 in Atlantic City. Dr. J. Arthur Myers is preparing a history of the College for our Twenty-Fifth Anniversary. A special feature of the history will include photographs of fathers and sons who are members of the College. If any of our father-and-son members have not sent their photographs to the Executive Offices in Chicago, they should do so without delay.

Mrs. Gordon joins me in sending you and your families our very best wishes for the New Year.

Burgess L. Gordon

PROGRESS REPORT ON TOKYO CONGRESS

Plans for the Fifth International Congress on Diseases of the Chest to be held in Tokyo, Japan, September 7-11, 1958, are well under way. Murray Kornfeld, Executive Director of the College, spent several weeks in Japan meeting with College officials in that country and with members of the Japan Chapter. A meeting of the chapter was held at Chinzanso, Tokyo on October 9, 1957. The meeting was attended by a large number of College members in Japan (see photograph), at which time plans for the Congress were reviewed and discussed. It was decided to hold the scientific sessions of the Congress in the Dai-Ichi Building which has two theaters seating 700 and 300 respectively. A separate room will be used for the continuous showing of motion pictures during the Congress. The secretariat of the Congress will also be established in the Dai-Ichi Building.

The Inaugural Session of the Congress will take place in the Yomiuri hall, and the closing banquet will be held at the Tokyo Kaikan. All of the abovementioned facilities are in the center of the city and within easy walking distance from the hotels.

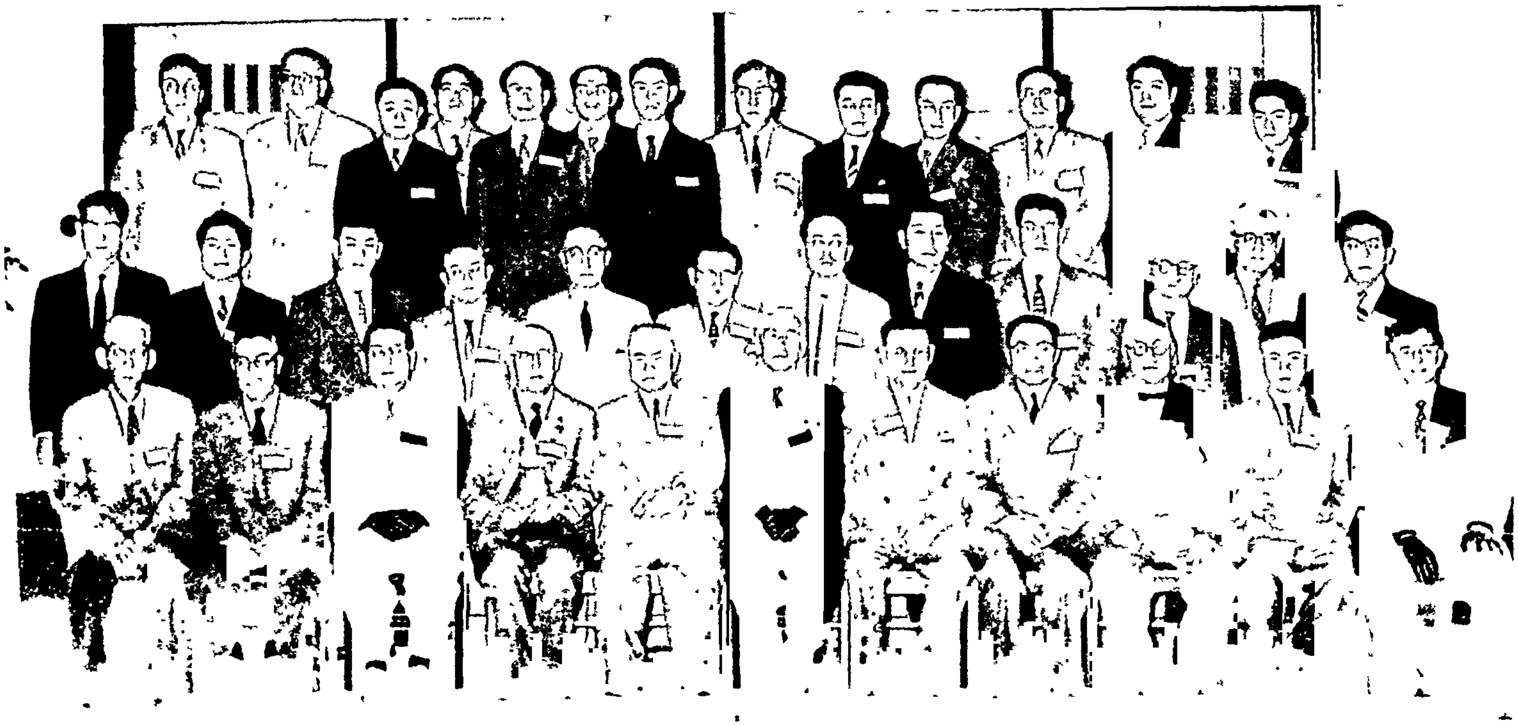
Arrangements are also being completed for technical and commercial exhibits.

The Imperial Hotel in Tokyo has been selected as the headquarters hotel to house the delegates and other first class hotels in Tokyo have been engaged for the Congress.

PRIME MINISTER OF JAPAN ACCEPTS HONORARY PRESIDENCY

Left to right: Prof. Jo Ono, Prof. Yoneji Miyagawa, Murray Kornfeld, Prime Minister Nobosuke Kishi, Prof. Taizo Kumagai, and Prof. Arao Imamura.

The Honorable Nobusuke Kishi, Prime Minister of Japan, agreed to serve as the Honorary President of the Fifth International Congress on Diseases of the Chest in Tokyo next September. A number of important officials in the Japanese government will be invited to serve with the Prime Minister as honorary members. All of the ambassadors residing in Tokyo will also be invited to serve as honorary members of the Diplomatic Committee.



Meeting of Japanese Chapter

Front row, left to right: Prof. Jiro Ishida, Tokyo District Chairman; Prof. Naotsugu Kawai, Chairman, Scientific Assembly; Prof. Masanaka Terada, Chairman of General Affairs; Prof. Yoneji Miyagawa, Vice President of the Congress; Prof. Taizo Kumagai, President of the Congress; Prof. Arao Imamura, President, Japan Chapter; Mr. Murray Kornfeld, Executive Director of the College; Prof. Jo Ono, Secretary General of the Congress and Regent for Japan; Prof. Hidejiro Haruki, Governor for Japan; Prof. Osamu Kitamoto, Chairman, Scientific Program; and Captain Ralph Volk, Chief of Medicine, U. S. Naval Hospital, Yokosuka.

OFFICERS AND COMMITTEES

The College has 132 members in Japan and every member is being assigned to serve on one of the many committees in order to facilitate the organization of the Congress. The President of the Congress is Professor Taizo Kumagai of Sendai University. The Vice Presidents are: Professors Hiroshige Shiota, Yoneji Miyagawa, Seizo Katsunuma, Arao Imamura, and Yas Kuno. Members of the Executive Committee are: Professors Masanaka Terada, Osamu Kitamoto, Masao Tsuzuki, and Naotsugu Kawai. Mr. Taizo Ishizaka, President of the Federation of Economic Organizations, one of the leading industrialists of Japan, is Chairman of the Committee on Finance. He is being assisted by Mr. Ichiro Yano, President of the Dai-Ichi Mutual Life Insurance Company. Professor Jo Ono, Regent of the College for Japan, is Secretary-General of the Congress.

SCIENTIFIC PROGRAM

Scientific papers, panel discussions, fireside conferences and motion pictures will be presented on the following subjects:

- Cardiopulmonary Function Studies
- Tuberculosis
- Coronary Disease
- Benign and Malignant Tumors
- Cardiovascular Surgery
- Bronchoesophagology
- Aviation Medicine
- X-Ray Radiation
- Cardiopulmonary Pediatrics
- Occupational Diseases of the Chest
- Asthma and Emphysema
- Miscellaneous Topics

Eminent scientists from countries throughout the world will participate in the discussions, which will be simultaneously interpreted into the three official languages of the Congress, i.e., Japanese, French and English. There will also be scientific and commercial exhibits and visits to various medical institutions and hospitals in Japan.

SOCIAL PROGRAM

An interesting program of social activities is being planned by the committee in Japan which will include official receptions, tea ceremonies served by Geisha girls, a Japanese kimono fashion show, flower arrangements, a Japanese musical, and special Japanese dining including tempura, Ghengis Khan, sukiyaki, etc. In addition, there will be tours arranged to view Mount Fuji, Shrines, Buddhas, Japanese gardens and parks, as well as other places of interest.

POST-CONVENTION MEETINGS AND TOURS

Following the close of the Congress in Tokyo, a group of physicians will leave for Kyoto to participate in the 7th International Congress of Bronchoesophagology sponsored by the International Bronchoesophagological Society. Dr. Chevalier L. Jackson, Philadelphia, serves as secretary of this society. In addition to the scientific program, plans are being perfected for a social program, as well as sight-seeing in and around Kyoto.

A side-trip to Nara, one of the national parks of Japan, will be arranged. The group will then proceed to Hakone where a limited number of rooms will be available at the Fuji Hotel. Hakone is one of the famous spas of Japan and is situated in one of the most beautiful mountain resort areas in the country. The group will then proceed via air to Hong Kong.

The programs which are being arranged by the College chapters in Hong Kong and the other countries to be visited at the close of the Congress in Japan will be covered in future issues of *Diseases of the Chest.*

For those planning to participate in the Grand-Congress Tour, it should be pointed out that the number will be limited to the first class accommodations and air transportation available. It is requested that they file their applications as soon as possible with the Executive Director of the College in Chicago.

INTERIM SESSION

The Interim Session of the College held at the Warwick Hotel, Philadelphia, on December 2 and 3, was one of the most successful and best attended fall meetings the College has ever had. More than four hundred members and guests were present for the scientific session presented on Monday, December 2, and the cocktail party and dinner that followed were attended by the maximum number of persons the hotel could accommodate. The Pennsylvania

Chapter of the College was host at the cocktail party. Dr. Burgess L. Gordon, President of the College, presided at the dinner and introduced the officials and guests. Mr. Robert K. Bell, Ocean City, New Jersey, Past President of the New Jersey State Bar Association and member of the House of Delegates of the American Bar Association, was guest speaker and gave a very interesting talk on "The Challenge to the Medical and Legal Professions." The evening closed with a series of Fireside Conferences on a variety of subjects of special interest to heart and lung specialists.

On Tuesday, December 3, the Executive Council, Board of Regents and Board of Governors held their semi-annual meetings, and a number of councils and committees of the College held special meetings during the day. The proceedings of the administrative meetings follow.

ADMINISTRATIVE SESSIONS

Warwick Hotel, Philadelphia

December 3, 1957

The following Regents, Governors, Chapter Officers and Council and Committee Chairmen attended the sessions of the College in Philadelphia:

Osler A. Abbott, Atlanta, Georgia
Albert H. Andrews, Chicago, Illinois
Alvan L. Barach, New York City
Gerald Beatty, Wilmington, Delaware
Samuel Bellet, Philadelphia, Pennsylvania
Otto L. Bettag, Chicago, Illinois
Katharine R. Boucot, Philadelphia, Pennsylvania
Otto C. Brantigan, Baltimore, Maryland
Charles A. Brasher, Mount Vernon, Missouri
John F. Briggs, St. Paul, Minnesota
Ross K. Childerhose, Harrisburg, Pennsylvania
Robert V. Cohen, Philadelphia, Pennsylvania
Sumner S. Cohen, Oak Terrace, Minnesota
Dean B. Cole, Richmond, Virginia
James P. Cooney (Maj. Gen.), Washington, D. C.
Edgar W. Davis, Washington, D. C.
Everett C. Drash, Charlottesville, Virginia
Seymour M. Farber, San Francisco, California
M. Jay Flipse, Miami, Florida
Carl H. Gellenthien, Valmora, New Mexico
Roy F. Goddard, Albuquerque, New Mexico
Alfred Goldman, Los Angeles, California
Alfred Goldman, St. Louis, Missouri
Burgess L. Gordon, Albuquerque, New Mexico
Edward A. Greco, Portland, Maine
J. E. J. Harris, Albuquerque, New Mexico
Chevalier L. Jackson, Philadelphia, Pennsylvania
Hollis E. Johnson, Nashville, Tennessee
Edward Lebovitz, Pittsburgh, Pennsylvania
Arthur M. Master, New York City
Robert L. Mayock, Philadelphia, Pennsylvania
Donald R. McKay, Buffalo, New York
Frank A. Merlino, Providence, Rhode Island
J. Arthur Myers, Minneapolis, Minnesota
Dan C. Ogle (Maj. Gen.), Washington, D. C.
Arthur M. Olsen, Rochester, Minnesota
J. Winthrop Peabody Sr., Washington, D. C.
Charles K. Petter, Waukegan, Illinois
Joseph C. Placak, Abingdon, Virginia
Coleman B. Rabin, New York City
Alfred A. Richman, New York City
Arnold B. Rilance, New Haven, Connecticut
Peter A. Theodos, Philadelphia, Pennsylvania
Howard S. Van Ordstrand, Cleveland, Ohio
David H. Waterman, Knoxville, Tennessee
Irving Willner, Newark, New Jersey
Roy A. Wolford, Washington, D. C.
Murray Kornfeld, Executive Director, Chicago, Illinois
Harriet L. Kruse, Executive Assistant, Chicago, Illinois
Margaret Rogers, Executive Assistant, Chicago, Illinois

JOINT MEETING, BOARD OF GOVERNORS AND BOARD OF REGENTS

A joint luncheon meeting of the Board of Governors and Board of Regents of the College was held at the Warwick Hotel, Philadelphia, on Tuesday, December 3, 1957. Dr. David H. Waterman, chairman of the Board of Governors, presided at the meeting. Dr. Robert V. Cohen, chairman of the program committee for the Interim Session of the College, was introduced and the members of the Board of Governors and Regents expressed their appreciation to him and his committee for the outstanding scientific program which had been presented on the previous day. Drs. Katharine R. Boucot and Robert L. Mayock, President and Secretary of the Pennsylvania Chapter of the College, were introduced and received the congratulations of the assembled officials for the splendid hospitality extended by the members of the Chapter.

The following reports were presented:

Report of the Committee on Scientific Program

24th Annual Meeting, San Francisco, June 18-22, 1958

Samuel Bellet, Chairman
Section on Cardiovascular Diseases

Peter A. Theodos, Chairman
Section on Pulmonary Diseases

Drs. Bellet and Theodos reported that plans for the scientific program to be presented in San Francisco are well under way and every effort will be made to complete the program promptly in order that it may be published in an early issue of *Diseases of the Chest.*

Report of the Committee on Membership

Chevalier L. Jackson, Chairman

Between March 1 and September 1, 1957, 333 applications from all parts of the world were received and presented to the Board of Regents. Of these applications, 162 were for Fellowship, 53 for Associate Fellowship, 82 for Associate Membership and 36 for advancement to Fellowship. Of this group, 166 applications were filed by physicians in the United States and Canada and 167 by physicians in other countries. It should be noted that the 167 applications from countries other than the United States and Canada include some 60 applications which were filed after the September 1 deadline. Twelve of the physicians in the United States and Canada who applied for Fellowship have been reclassified as Associate Fellows. These applications were handled promptly in order to be able to include the listings in the 1958 edition of the Directory of the College.

With the addition of 294 new members in all parts of the world, the total membership of the College is now 6166. As of November 15th, there were 45 applications pending presentation to the Board of Regents at the Annual Meeting. Others will, of course, be received between now and March 1, 1958.

Report of the Editorial Board

J. Arthur Myers, Editor-in-Chief

The Editorial Board is pleased to report on the progress of *Diseases of the Chest* for the year 1957. During the year, approximately 80 per cent of the space in the journal was devoted to the publication of scientific articles and College news. We published 154 scientific articles in 1957, as compared to 141 in 1956.

The current circulation of the journal is 8,100 copies monthly which reach 88 countries and territories throughout the world. Effective January, 1958, with the addition of new members, the circulation will reach 8,400 copies monthly which will be the largest circulation the journal has enjoyed.

Report of the Board of Examiners

Coleman B. Rabin

Twenty-one candidates for Fellowship in the College are being examined in Philadelphia today. Of these, 4 are retaking the examination at the request of the Board of Examiners.

We have 72 other members to be examined and it is expected that the majority of these will take the examinations in San Francisco next June. They will be classified as Associate Fellows until they have successfully completed the examinations.

Report of the Council on Postgraduate Medical Education

J. Winthrop Peabody Sr., Chairman

Three postgraduate courses on diseases of the chest were presented by the College this fall: The 12th Annual Chicago Course was held at the Hotel Knickerbocker, October 21-25, in which 53 physicians were registered; the 10th Annual New York City Postgraduate Course, November 12-16, was presented at the Park Sheraton Hotel and registered 119 physicians; and the 3rd Annual California Course was held at the Ambassador Hotel in Los Angeles, December 9-13, with a registration of 104. Our Council is pleased to report that the 11th Annual Postgraduate Course on Diseases of the Chest will be presented in Philadelphia, March 3-7, at the Warwick Hotel, and the 4th Southern Postgraduate Course is scheduled to be held at the Grady Memorial Hospital, Atlanta, Georgia, in cooperation with Emory University, during the week March 10-14, 1958.

During the period from 1946 through 1957 the College has presented fifty postgraduate courses on diseases of the chest in the United States with the registration totaling 3,533. This is in addition to the many fine postgraduate courses presented under the auspices of College chapters in other countries. It is the aim of your Council on Postgraduate Medical Education to continue this teaching program in order that many more physicians may avail themselves of the opportunity to keep abreast of the advances made in the diagnosis and treatment of heart and lung conditions.

Report of the Committee on Bronchoesophagology

Arthur M. Olsen, Chairman

Since the annual meeting of the College in June, the Committee on Bronchoesophagology has been increased in size by the addition of 5 new members. The full membership of the committee now totals 15.

During the past year the major project of the Committee on Bronchoesophagology has been a study on bronchography. This study was carried out by means of personal communication with 57 men who make bronchograms. These men were drawn from the specialties of radiology, thoracic surgery and ENT (bronchoesophagology). The report was given as part of the scientific program at the annual meeting of the College in May, 1957 and will be printed soon in *Diseases of the Chest.*

At its recent meetings the committee has considered and discussed at length a variety of subjects within the field of bronchoesophagology. These include (1) problems in the training of bronchoesophagologists (editorial *Diseases of the Chest*, December, 1955), (2) bronchography, (3) complications of esophagoscopy and bronchoscopy and their prevention, (4) foreign bodies—who will remove them?, (5) anesthesia for peroral endoscopy, discussion of an analysis of various agents, (6) endoscopic photography in the teaching of bronchoesophagology, (7) esophageal motility studies, (8) study of bronchial anatomy and bronchial nomenclature, (9) cinematography of the esophagus.

As a project for 1958 we are planning to prepare an editorial which will call attention to the value of endoscopic photography in the teaching of bronchoesophagology. Although we do not expect to make bronchoesophagologists out of medical students, we do feel that they should be thoroughly acquainted with the field so that many of them can take up the specialty at a postgraduate level.

Report of the Committee on Cardiovascular Disease

Arthur M. Master, Chairman

The Sections on Cardiovascular Disease of the American College of Chest Physicians can look forward to making significant contributions to progress and education in their respective fields. The possibilities are manifold. The chief reason for my confidence is the fact that the country's best cardiologists are now enrolled and actively participating in our organization.

There are now seven sections in Cardiovascular Disease:

Section on Clinical Cardiovascular Disease
Eliot Corday, Beverly Hills, California, Chairman

Section on Angiocardiography
Israel [illegible]k, N. Y., Chairman

Section on Cardiovascular Surgery
Charles P. Bailey, Philadelphia, Pennsylvania, Chairman

Section on Rehabilitation
H. Easton McMahon, New York, N. Y., Chairman

Section on Electrocardiography
Irving Mack, Chicago, Illinois, Chairman

Section on Cardiovascular Physiology
John J. Sampson, San Francisco, California, Chairman

Section on Pediatric Cardiology
Benjamin M. Gasul, Chicago, Illinois, Chairman

I respectfully suggest that there is a need for two more sections to be constituted; one on "Hypertension" and another on "Roentgenography of the Heart." The latter group could probably operate within the framework of the already active Section on Angiocardiography or vice versa.

It is important that the programs of all these sections be coordinated, and this can best be done at a Chairmen's meeting held at least twice yearly. In the past, this has not worked out as well as it might. It would probably be most convenient for such conferences to be held at the annual meeting place and in Chicago.

To my mind, a most valuable project for us to concentrate on would be, in broad terms, "Recent Advances in Cardiovascular Diseases." This would include progress in diagnostic techniques, therapy, changing patterns of disease, etc., all of which would be culled from the many contributions made at our own meetings.

We should plan to have certain topics pre-selected by the program committee, covered thoroughly from every aspect at each of our annual and interim meetings. This need not interfere with the plans of any contributor to publish his own work independently, if he so wished.

The chairmen of the sections on cardiovascular disease, the program committees wh[illegible]la of the Seminars, Scientific Lectures, Luncheon Panels and [illegible] at the annual meetings, would delineate the scope of "recent advances in cardiovascular diseases, medical and surgical," always correlating with pulmonary disease, whenever possible. Symposia on pertinent, provocative, up-to-the-minute problems of cardiovascular disease, both from the medical and surgical viewpoint, should be planned. These should deal, not only with current progress but indicate the direction of future research.

Thus, a *Seminar* on a topic such as *angina pectoris due to coronary disease* would include a physician to review the problem of chest pain, and another physician to relate the natural history of angina pectoris. After all, there must be control data in order for the surgeons to evaluate old and new operative procedures which they, of course, would present. There is now extant a fairly good natural history of angina pectoris, e.g., White and Bland; Weiss and Weiss; Master, Jaffe and Dack; insurance material and others. The surgeons would submit the latest in their procedures for the alleviation or cure of coronary disease.

There are many similar timely topics with their dramatic and kaleidoscopic advances from which to choose. To mention but a few, extracorporeal circulation for open heart surgery; the surgical correction of aortic stenosis; or aortic insufficiency; left heart catheterization; angiocardiography and roentgenography in the diagnosis of congenital and acquired heart disease; serum enzyme determinations in myocardial necrosis, all lend themselves for review both by internists and surgeons. Wherever indicated, the natural course of the disease would first be described, e.g., in aortic stenosis and also in aortic insufficiency.

The SGO-T determination is replacing the sedimentation rate test. In fact, in my opinion, the latter is useless in coronary artery disease but the transaminase reading is becoming invaluable for determination of myocardial injury. In acute coronary insufficiency, it would be particularly useful. Again, Isuprel and adrenal corticosteroids in heart block; new antihypertensive therapy, normal blood pressure from birth to old age; are all of interest and of paramount importance to the up-to-date internist. In summary, then, the "headlines" in medicine would be surveyed at our annual and interim meetings.

The *Scientific Sessions* program would be similarly planned with the same general topics. Not only would the speakers submit papers in advance but the discussors, too. If they wish, the latter could alter their 5 minute paper after the meeting, if a change is desired.

The *Round Table Luncheon Meetings* would be programmed, again, with at least a few definitely chosen topics in mind. The 4 or 5 speakers would prepare 10 minute papers in advance. Stenographic records could be made and later edited, of the questions and answers following the 10 minute talks, or the moderator or an associate moderator could jot these down. If the moderator insists, as he should, on brief, succinct, interrogation and the same type of reply, much territory will be covered. The questioner should not be permitted to make a speech, nor to ask a "discuss" type of question. Thus, the formal written talks, and the questions and answers which follow, would constitute a good review and help round out similar contributions in the seminars and in the scientific sessions.

Fireside Conferences can also, in part, be designed to survey the major topics chosen for the particular annual or interim session or sessions. One or two volunteers would be given pad and pencil and the discussion leader could always briefly repeat the question to him and briefly summarize each answer. I find I do this naturally at most such conferences.

Our *Council on Undergraduate Medical Education* might take advantage of much of the material and organize a teaching project on the undergraduate level, derived from these planned topics.

In conclusion, then, without belaboring these ideas any further, I am confident that much can be done by the American College of Chest Physicians through the Sections on Cardiovascular Disease. With planned initiative and imagination on our part, medicine will look to the American College of Chest Physicians for leadership in teaching and research.

Report of the Committee on Pulmonary Diseases in Children

Roy F. Goddard, Chairman

The Committee on Pulmonary Diseases in Children was created at the Interim Session of the College held in Seattle in December, 1956 with a membership of five. Informal meetings of the committee were held in Chicago in January and October, and the first annual meeting was held in New York City in June of 1957, during the 23rd annual meeting of the College. The committee has now been enlarged to 26 members. A good number of members were present for our committee meeting held today.

Among the projects of our committee for the coming year are the following: 1) Pulmonary function in the toddler age group (1-6 years); 2) Continuing studies on mechanics of breathing in the newborn and pulmonary function studies in older children; 3) Benefit of certain surgical procedures in improving pulmonary function in children with poliomyelitis and other respiratory disorders. The committee is also cooperating with the Committee on Scientific Program in planning for the discussion of pulmonary diseases in children at the next annual meeting of the College.

The committee has recommended the reappointment of Dr. Milton Levine, New York City, as representative to the 1960 White House Conference on Children and Youth.

We believe that the past six months has seen considerable new interest stimulated in pulmonary problems in children and the beginning of an active group to carry out the functions and objectives of the committee outlined in our first report to the Board of Regents last June.

Report on College Books

Clinical Cardiopulmonary Physiology

Burgess L. Gordon, Chairman, Editorial Committee

It is gratifying to report that over 2,000 copies of the book have been sold during the past year, since its publication early in 1957. We have been advised by Grune & Stratton, Inc., the publishers, that they are negotiating with foreign publishers relative to translation and publication of the book in other countries.

Roentgenology of the Chest

Coleman B. Rabin, Chairman, Editorial Committee

We have been informed by the publisher, Charles C Thomas, that our new book will be available in February. It is anticipated that the book will have between 500 and 600 pages; the book will have many excellent illustrations and the format we believe is most attractive and the text easily read. This book, we are sure, will be a credit to the growing list of books published by the College and we anticipate that it will be well received.

SEMI-ANNUAL MEETING, BOARD OF REGENTS

The Board of Regents of the College held its semi-annual meeting on Tuesday afternoon, December 3, at the Warwick Hotel, Philadelphia. Dr. John F. Briggs, chairman, presided.

Dr. Petter, Treasurer of the College, presented the financial report and 1958 budget which were unanimously accepted. The report of the Committee on Insurance was referred to committee for further study.

Dr. Childerhose reported for the Committee on Medical Practice, on which he serves as vice-chairman. The committee will convene in San Francisco to give further study to their program.

Colonel James A. Wier, chairman of the Committee on Chemotherapy and Antibiotics submitted a report to the effect that they plan to complete the report on the chemotherapy of non-tuberculous diseases of the chest and have it ready for publication shortly. The report was revised at the annual meeting of the committee in New York and a new draft has been completed. At present it is being submitted to the committee members for comments and approval.

The following report received from Dr. Alexander Libow, chairman of the Committee on Non-Surgical and Drug Therapy, stated: It has been the custom of this committee to review current therapy in pulmonary tuberculosis every five years. This has been accomplished by presenting ten standard cases to one hundred participating chest physicians from all parts of the country. The same ten cases are to be presented, with changes in therapy, and the comments of the participating physicians are compared with each other and with the previous five year report. It is almost five years since the last report was published and the committee plans to present this work once more. Several other projects under consideration by the committee are "Use of Bed Rest in the Treatment of Tuberculosis," "Treatment of Tuberculosis in Out-Patient Clinics," and the "Home Treatment of Tuberculosis." Other projects will undoubtedly be suggested by members of the committee and they will be explored.

Dr. Robert J. Anderson, chairman of the Council on Public Health, submitted the following report: The Council on Public Health proposed to prepare timely articles on respiratory disease subjects to the membership through *Diseases of the Chest.* Influenza caused by Asian A virus was the subject of the first article which was presented in the August issue of the College journal. This was one of the first reports to appear in scientific journals regarding this problem. As all of the members well know, the problem is still with us but I believe it is at its peak at this time and we look forward to a falling incidence very soon. Some areas of the country have already experienced the full impact of the epidemic. Several things are noteworthy in this epidemic. It was forecast quite accurately with the exception that the peak was reached slightly earlier than was expected. Advance preparations were initiated by the medical and public health professions which I am sure have blunted the impact of the epidemic. The additional mortality of the epidemic has been small as a consequence. The opportunity for research upon influenza has been seized by the investigators of the Public Health Service, the Armed Forces, and the universities over the country, so that we shall be better prepared to act when the next influenza epidemic appears on the horizon. The Council on Public Health will try to keep the membership informed and alerted to respiratory disease problems of interest to the membership.

Dr. Alfred Goldman (Los Angeles), chairman of the Committee on Pulmonary Surgery, reported that his group has been concerned with the collection of approximately 1000 cases of mass x-ray survey type malignant neoplastic lesions of the lung (coin lesions). The cure rate of this type of lesion by surgical resection is still unknown. The published reports of a small series of such lesions resected indicate that there is a large increase in the 5 year survival rate compared to the 5 year survival rate of cancer of the lung not discovered in its asymptomatic early stage. By collecting data on a large series of this type of early asymptomatic cancer of the lung surgically resected, a more accurate appraisal of the 5 year survival time can be made. It is anticipated that a complete report of our study may be available by the time of our annual meeting in San Francisco next June.

The following report was submitted by Dr. Arthur W. Dahlstrom, chairman of the Committee on Indian Affairs, concerning the New Mexico Field Tuberculosis Study: *There is little to report on the progress of the study program to date. Influenza has interfered with the tuberculin testing of the group that has this fall completed the therapy. The last of the 20 schools will be tested December 2. The figures are being assembled and the control-placebo code will then be opened and the results tabulated and sent to the university for evaluation. The larger group will have completed their therapy next spring. It is hoped that some definite figures will be available by the time of the next annual meeting in San Francisco.*

Dr. Robert B. Stone, chairman of the Committee on Audiovisual Aids, advised the Board that his committee is assembling a new collection of 35 mm lantern slides which may be used for teaching diseases of the chest to undergraduate medical students. It is hoped that the collection will be completed prior to the annual meeting of the College in San Francisco and may be exhibited at that time.

The following resolutions were presented and approved:

WHEREAS, The American College of Chest Physicians is an international organization with more than 6,000 members in 86 countries and territories, and

WHEREAS, The College has organized, since 1950, four successful international congresses on diseases of the chest, and The Fifth International Congress of the College will be held in Tokyo, Japan, September 7-11, 1958, and

THEREFORE BE IT RESOLVED, That the Board of Regents of the College authorize the establishment of international committees to provide further opportunities for our members throughout the world to contribute to the advancement of the College program, and

WHEREAS, Most of the work of the College is conducted through its councils and committees,

BE IT FURTHER RESOLVED, That these international committees shall meet at the time and place of the international congresses sponsored by the American College of Chest Physicians, and

BE IT FURTHER RESOLVED, That the President of the College be authorized to appoint such committees.

WHEREAS, The Research and Education Foundation for Chest Disease has been reorganized according to a resolution adopted by the Board of Regents of the College at its last annual meeting in New York City, June, 1957, and

WHEREAS, It has taken several months to conduct the reorganization and preparation of literature for the foundation, and

WHEREAS, A great deal of the preliminary work essential to the raising of funds for research has been accomplished, and

WHEREAS, The initial appropriation of $5,000.00 has been utilized for this purpose, and

WHEREAS, It is requested that an additional sum of $5,000 be appropriated for the Foundation by the Council on Research of the College, and

WHEREAS, Mr. Ward Bentley, the Executive Secretary of the Foundation, has expressed an opinion that there is every possibility, given more time, for the Foundation to succeed in its efforts to raise research funds,

THEREFORE BE IT RESOLVED, That the Council on Research of the American College of Chest Physicians advance $5,000.00 of its funds to the Research and Education Foundation for Chest Disease for the purpose of defraying the cost of its operation during the year 1958, and

BE IT FURTHER RESOLVED, That the Council on Research be authorized to enter into negotiations with Mr. Ward Bentley for a retainer fee for this period of time.

Mr. Kornfeld reported on his recent trip to the Orient and acquainted the members of the Board of Regents with the arrangements that have been completed for the Fifth International Congress on Diseases of the Chest to be held in Tokyo, September 7-11, 1958. The first article dealing with the Congress in Tokyo and the post-congress tour of Japan appears in this issue of the journal. Additional articles concerning the congress and the post-congress tour will be published in future issues.

COLLEGE ANNOUNCES NEW CARDIOVASCULAR SECTION

We wish to announce, effective with this issue, the Section on Cardiovascular Diseases which will appear as a regular feature in *Diseases of the Chest.* We trust that College members and subscribers to our journal will be pleased with this new section and the Editorial Board invites comments and suggestions.

It is the objective of the Editorial Board to keep the material published in *Diseases of the Chest* current and of interest to our readers and we trust that the addition of this new section will add another milestone in the progress being made in the specialty of chest diseases.

College Chapter News

NEW ENGLAND STATES CHAPTER

The New England States Chapter will present the following scientific program at its meeting to be held on January 11, 1958, at the Dowling Amphitheater of the Boston City Hospital:

9:00 a.m. Registration

9:30 a.m. "Antimicrobial and Steroid Therapy in Diseases of the Chest: Resident Organisms—Staphylococcus Infection-Influenza, 1957" (panel)

Moderator: Maxwell Finland, Boston

Panel: Edward H. Kass, Calvin N. Kunian, Christopher Martin, and Louis Weinstein, Boston

11:00 a.m. "Stump the Experts" (x-ray panel)

Moderator: Max Ritvo, Boston

Panel: S. Clive Cohen, James B. Dealy, Jr., Richard H. Overholt, and Stanley M. Wyman, Boston

12:30 p.m. Luncheon and visit to the research laboratories of the Boston City Hospital

2:00 p.m. "Airspace Disorders" (panel)

Moderator: John W. Strieder, Boston

Panel: Theodore Badger, Edward A. Gaensler, Joseph P. Lynch, and Lamar Soutter, Boston

"Chronic Dyspneic Diseases—Physiology and Treatment" (panel)

Moderator: Maurice S. Segal, Boston

Panel: Ernst O. Attinger, Boston; Alvan L. Barach, New York City; Jeremiah E. Greene, Boston; and Edwin R. Levine, Chicago

5:30 p.m. Cocktail party and dinner, Harvard Club

NEW CHAPTER OFFICERS

NEW ENGLAND STATES CHAPTER

President: Maurice S. Segal, Boston, Massachusetts
1st Vice-President: Joseph N. Corsello, Providence, Rhode Island
2nd Vice-President: Francis D. T. Bowen, Hartford, Connecticut
Secretary-Treasurer: S. Clive Cohen, Boston, Massachusetts (re-elected)

SOUTHERN CHAPTER

President: Joseph S. Cruise, Atlanta, Georgia
1st Vice-President: Daniel E. Jenkins, Houston, Texas
2nd Vice-President: John H. Seabury, New Orleans, Louisiana
Secretary-Treasurer: DeWitt C. Daughtry, Miami, Florida

PUERTO RICO CHAPTER

President: Jose L. Porrata, Hato Rey
Vice-President: Jose Amadeo, Aibonito
Secretary-Treasurer: Hilarion Sanchez, Rio Piedras

NEWS NOTES

Dr. Joseph B. Stocklen, Cleveland, Ohio was awarded the Dearholt Medal, the highest award given by the Mississippi Valley Conference on Tuberculosis. The medal is awarded to an individual for outstanding contributions to tuberculosis control.

Dr. Jay Arthur Myers, Minneapolis, Minnesota, Editor-in-Chief of *Diseases of the Chest,* received the William A. Howe Honor Award from the American School Health Association at the annual banquet of the association held in Cleveland, Ohio, November 13.

Dr. William H. McCain, formerly internist at St. John's Sanatorium and Crippled Children's Hospital in Springfield, Illinois, has been appointed Medical Director of the Hillcrest Sanatorium, Quincy, Illinois.

Prof. Manoel de Abreu, Rio de Janeiro, Brazil, Regent of the College, was honored on his birthday, January 4, by the Paulista Association of Chest Diseases in Sao Paulo, his birthplace. This date has been officially set aside as the "Day of Abreugraphia" in homage to Prof. de Abreu whose research and eventual development of the 35mm film marked the beginning of mass chest x-ray as we know it today. The association plans to celebrate this date annually and will present a scientific program dealing with the fight against tuberculosis.

The following Fellows of the College were recently appointed by William G. Stratton, Governor of the State of Illinois, to the advisory committee on tuberculosis, which serves as an advisory body to the tuberculosis control service of the state: **William E. Adams**, Chicago; **Eugene J. Des Autels**, Hines; **Leonard Krasner**, Downey; **Hiram T. Langston**, Chicago; **William Lees**, Chicago; **Dan Morse**, Peoria; **Julius B. Novak**, Chicago; **Edward A. Piszczek**, Chicago; and **George C. Turner**, Chicago. Drs. **Kenneth G. Bulley**, Aurora; **Clifton Hall**, Springfield; and **David B. Radner**, Chicago, were re-appointed to the committee.

Dr. Otto L. Bettag, Chicago, Director of Public Welfare for the state and Regent of the College, and **Dr. Ernest Teller**, Chicago, Chief of the Tuberculosis Control Service, serve as ex-officio members. Dr. Bettag was also reappointed by Governor Stratton to a second term as member of the Medical Center Commission.

MEDICAL SERVICE BUREAU

POSITIONS WANTED

Internist and physiologist, eligible for American Board of Internal Medicine examination, Ph.D. (physiology) with 7 years' experience in research in respiration and circulation, trained and experienced in pulmonary function testing; experience as staff member, tuberculosis sanatorium; presently member of faculty of grade A medical school, desires position in which clinical medicine and clinical research can be combined in above fields of interest. Please address inquiries to Box 296B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

DISEASES of the CHEST

VOLUME XXXIII FEBRUARY, 1958 NUMBER 2

Inhalation Hazards in Nuclear Energy Programs*

Stable Elements

G. W. H. SCHEPERS, M.D., D.Sc., F.C.C.P.**
Saranac Lake, New York

The continuing, far from dispassionate, public debate over the effects of nuclear tests on the health of future generations of mankind has fortunately focused attention on the need for control of a potential man-made environmental hazard probably even before it has become a reality. The current program of atom and hydrogen bomb manufacture will perhaps only be terminated when one of the militant human factions stumbles onto a yet more effective, if not more dreadful, method of subduing its adversaries or when extra terrestrial adventures pre-empt the unified resources of all mankind. We may as well attempt meanwhile to discover how to live with the bombs. This will only become possible if we recognize all the possible modes of exposure, have precise knowledge about the nature of the injury to be anticipated, and understand what the permissible toxicity tolerances will be.

For the present the major concern is over the effects of radiation, and most emphasis is placed on the hazard associated with radioactive "fallout" following thermonuclear detonations. It will be a pity if pre-occupation with the political significance of the armaments race causes us to lose sight of the potential harm which may attend the peaceful applications of nuclear energy. During the stalemate which will result when all opposing nations have each perfected enough bombs mutually to destroy each other's cities in one single holocaust, reactors of ever increasing power and diversity will be built in growing numbers and at diverse places across the surface of this globe. The creation of these atomic powered units and their subsequent operation or periodic dismantlement may, but need not, bring health hazards even greater than those attributed to the bombs which sensible politicians will keep safely locked away as long as possible. Fortunately, the issue being in the domain of mathematics, physics, and chemistry there should be an engineerable remedy for each predictable danger.

Some of the non-radioactive substances which play a part in the nuclear energy programs are capable of producing tissue effects of unusual complexity and ominous portent. Fortunately, as compared with the fantastic biological scope of radioactive elements, there seems as yet to be a limit

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*Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.

**Formerly Director, Saranac Laboratory. Presently at: Institute of Industrial Health and Department of Pathology, University of Michigan, Ann Arbor.

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to the range of stable elements which may prove dangerous to man. It *may come as a surprise to many, however, to ascertain the full extent of* the nocuous environmental factors to which human beings may already be exposed, in the generation of nuclear power, during the stages preceding the achievement of radioactive energy. Figure 1 emphasizes the fact that, despite all that is already known about occupational diseases, there are so many mineral substances whose biological effects remain unknown that we have no means of predicting the nature of future hazards. The atomic age has rendered important a great many minerals and elements which previously had no health relevance for man. The present account is limited to respiratory system hazards, and therefore will deal with part of the problem only.

Sources of Exposure

Mining and Transportation of Raw Materials:

In gathering the raw materials needed for the production of nuclear energy, almost the full range of human occupations plays a part. Most of the attendant hazards are not new. Some activities are surprisingly mundane, e.g., collecting bones of deceased animals on the Transvaal High-

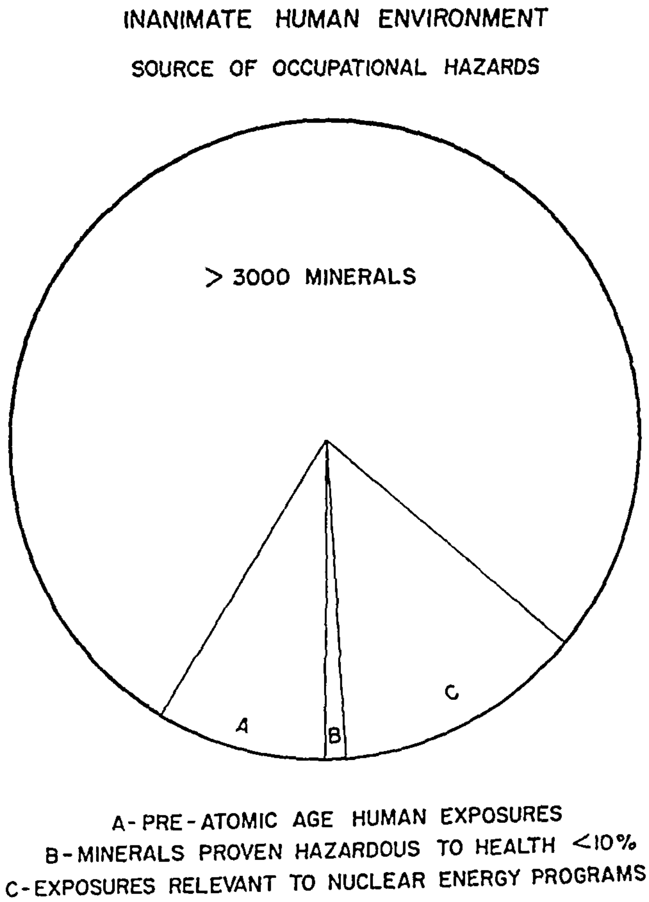
INANIMATE HUMAN ENVIRONMENT
SOURCE OF OCCUPATIONAL HAZARDS
> 3000 MINERALS
A
B
C
A-PRE-ATOMIC AGE HUMAN EXPOSURES
B-MINERALS PROVEN HAZARDOUS TO HEALTH <10%
C-EXPOSURES RELEVANT TO NUCLEAR ENERGY PROGRAMS

FIGURE 1: Diagram showing the ratio of known hazardous mineral substances to the whole mineral kingdom, and forecasting the range of new minerals to which human beings will be exposed as a result of the mining activities necessary to projected nuclear energy programs.

veld. Others are highly eclectic, e.g., isolation of heavy water. In essence, however, the main respiratory hazard during this stage derives from mining. As silica forms a major constituent of the earth's crust, and as the minerals which are of importance to atomic energy programs are embedded within a diversity of rock formations, silicosis once more asserts itself as a relevant health hazard. In mines, such as those in South Africa, where the recovery of uranium has been profitably added to the quest for gold, no new hazard has necessarily arisen. As the value of the uranium increases and that of the gold declines, fuller recognition will have to be accorded to the relationship of the residual pulmonary health problem to the atomic energy program. Hundreds of miners annually develop silicosis or its complications, chiefly tuberculosis, in the South African mines, despite energetic engineering and medical efforts to prevent these diseases. A great deal of progress has been made in reducing the ravages of dust-caused disability and death.[1] There is not yet in sight any hope of conquest of this problem, and at least some of the progress made may have been illusory for there has been a steady shift of the clinical emphasis from mere radiographically demonstrable pneumoconiosis to pulmonary disability as the dominant issue.[2]

The demand for uranium is so tremendous that new mining ventures have been initiated in almost every section of the globe. Most of the new mines have started off as small operations exploring promising ore bodies. Many amateurs have taken part in these pursuits and there is reason to believe that proper dust hygiene measures have not always been observed. Undoubtedly when the effects of excessive quantities of inhaled rock dust commence to show, we shall yet encounter some of the victims of these earlier undisciplined enthusiasms. It is just as well that more physicians appreciate what constitutes silicosis.

In at least one other region the search for uranium has stirred up an old problem. At Schneeberg and Joachimstal in the Carpathian mountains, now behind the Iron Curtain, the mines, which for centuries have yielded abundant uranium, cobalt, and arsenic, have over the years acquired such a bad reputation as health hazards that the popular designation for these ancient mines has long been "the death shafts."[3] Much of the evil reputation of these pits probably reflects earlier inadequate hygiene standards and it is to be hoped that the Russian technologists have since overcome this problem. However, the high pulmonary cancer rates in these mines has focused attention on the possible pathogenic role of minerals other than silica, for it is fairly well established[4, 5] that inhaled quartz dust is not carcinogenic. Speculation has ranged from the role of the radioactive uranium and the specific influence of cobaltic compounds to the neoplasiogenic potency of arsenious acid released by subterranean fungi.

The foregoing issue illustrates the general problem. Besides the known hazard constituted by inhaled crystalline free silica we are today faced with the problem of defining the precise biological action of a great many minerals associated with radioactive ore bodies. A conservative estimate of the number of minerals to which human beings may theoretically be exposed through the expansion of modern industry, exceeds 3,000 separate varieties.[6] The demand for uranium, strontium, and lithium has already brought miners into contact with a considerable number of minerals additional to those previously encountered as an environmental health hazard in the process of catering to civilization's basic raw material needs. The problem is even broader than this.

For making a hydrogen bomb or to build a reactor, far more elements are exploited than merely the well publicized ingredients, uranium, strontium, lithium, or deuterium. Thermonuclear bombs, radiant energy reactors and intercontinental ballistic missiles are man's highest technological achievements. To create these, not only the immediate active elements are needed, but also a host of ancillary substances which either are a material factor in compounding the final product or serve a useful purpose at an intermediate stage. Substances such as beryllium, boron, graphite, zirconium, lead, and mercury all play a substantial role. In gathering together all these elements, diversified mining activities are involved. Bombs and reactors also have created problems in structural engineering. Vast caverns have been hollowed out in volcanic rock, both as storage depots and for the reception of radioactive wastes. Rocks have been crushed and pulverized to make concrete. Asbestos and glass wool have been invoked as insulating materials. In the meanwhile, the range of useful products is continually being expanded by the discoveries of the research chemists and physicists. The rare earths, once so truly rare, are currently being advertised as available by the carload. Garnering these diverse products devolves on the activities of miners. These men therefore form the first phalanx of those who may theoretically be exposed to non-radioactive respiratory tract hazards in the diversified atomic energy programs.

Metallurgical and Chemical Processes:

The next phase of the problem is encountered in the plants where the desired elements are recovered from ore bodies, refined, and subsequently compounded or alloyed as required for specific purposes. The potential health hazards in this phase are great and literally volumes have been written about experiments to track down the toxicity of single elements and their compounds.[7, 8]

Uranium has for some time served as the classical example. For the present purpose we are not concerned with its radioactive properties. The principal uranium ores are pitchblende, carnotite, autunite, and tobernite. The former two are the more important. In pitchblende the uranium oxide content may range from 10 to 70 per cent. Other elements which may be present are radium, lead, aluminum, arsenic, calcium, iron, magnesium, manganese, nickel, cobalt, molybdenum, sulphur, fluorine, silicon, titanium, sodium, carbon, helium, hydrogen, oxygen, cadmium, phosphorous, chlorine, osmium, palladium, platinum, copper, and various of the rare earths. The uranium usually occurs in the form of UO_2 and UO_3 in ratios which correspond closely to U_3O_8. Carnotite has been given the formula: $K_2O \bullet 2UO_3 \bullet V_2O_5 \bullet 3H_2O$. While the potassium and vanadium form the dominant constituents, lead, radium, barium, and calcium are prominent constituents and traces of numerous other elements also are present. In autunite, calcium and phosphorous, and in torbernite, copper and phosphorous are important constituents. From the foregoing it should be clear, therefore, that in coping with inhalation problems linked with uranium ore dust, the uranium may be the dominant agent or may be the lesser constituent.

The extraction of uranium from its ores is done largely by means of nitric and hydrochloric acids. The uranium is released from the uranyl nitrate by ether. Being multivalent, the liberated uranium forms compounds with valence dominances of 3, 4, 5, or 6. The hexavalent uranium is most stable in aqueous solutions. Of the various compounds to which human exposures may occur, the oxides (UO_2, UO_3, UO_4, $UO_4 \bullet 3H_2O$, U_3O_8), fluorides (UF_4, UF_6, UO_2F_2), diuranates ($Na_2U_2O_7 \bullet 1\text{-}\frac{1}{2}H_2O$, $(NH_4)_2U_2O_7 \bullet 4H_2O$), chloride ($UCl_4$), nitrate ($UO_2(NO_3)_2 \bullet 4H_2O$) are best known. There naturally are numerous other compounds, such as the hydride (UH_3), carbides (UC, U_2C_3, UC_2), nitrides (UN, $UN_{1.5\text{-}2}$), acetate ($UO_2(C_2H_3O_2)_2 \bullet 2H_2O$) etc., which may be of importance at some other stage.

The diversity of problems encountered may be illustrated by means of yet another element which is of crucial importance in practically all phases of atomic energy production. Because of its peculiar lattice structure, beryllium is uniquely valuable as a source of neutrons, particularly as it remains stable at the high temperature generated under nuclear bombardment. This use has greatly augmented the exploitation of the element. Prior to 1931 less than 100 pounds of the metal were consumed annually for all industrial purposes in the United States. Ten years later the annual consumption approached 30,000 pounds. By 1950 this use had increased a further five-fold (approximately 150,000 pounds). Recent estimates predict that by 1960 more than a million pounds of beryllium will be needed to support the nuclear reactor programs in addition to the multifarious metallurgical uses of the element (Fig. 2).

Beryllium is extracted chiefly from beryl (beryllium aluminum silicate). The beryllium content of the ore varies between 10 and 13 per cent. About 15 to 20 per cent of the ore is aluminum and 65 to 70 per cent is silicon dioxide. To reduce the ore to beryllium oxide either a sulphate or a fluoride process may be used. Several other variations are also invoked for special purposes. During these phases plant personnel may thus become exposed not only to the milled ore dust but also to compounds such as beryllium oxide, beryllium sulphate, beryllium fluoride, beryllium oxyfluoride, basic beryllium carbonate, beryllium phosphate, beryllium chloride, beryllium nitrate, and beryllium stearate. The final product, of course, is the beryllium metal. This is the form in which the element is used for atomic energy purposes. Before it can be made available, many inhalation exposures would be possible if inadequate hygiene precautions are exercised.

The list of "new" elements which yield health problems between the phase of mining and the application of the substance in bombs or reactors is growing steadily. In practically all instances the elements are refined to their pure state and new compounds are manufactured. Thus series of wholly artificial hazards may be created.

Bomb Manufacture and Reactor Installation

For security reasons many of the phases involving the use of specialized materials in the manufacture of thermonuclear weapons remain undisclosed. The role of radioactive materials also predominates during this phase. However, it is no secret that the plutonium, the lithium and the beryllium have to be housed in appropriate containers, and it takes but little imagination to recognize that in some measure certain metallic constituents of these bombs have to be machined or welded with the sequential release of respirable particles or fumes.

The principles of construction of reactors are a little better known. Even high school students are aware of the role of the graphite cores of the atomic piles, the significance of special metallic coolants (e.g., sodium), the value of lead shielding, etc. Any constructional process

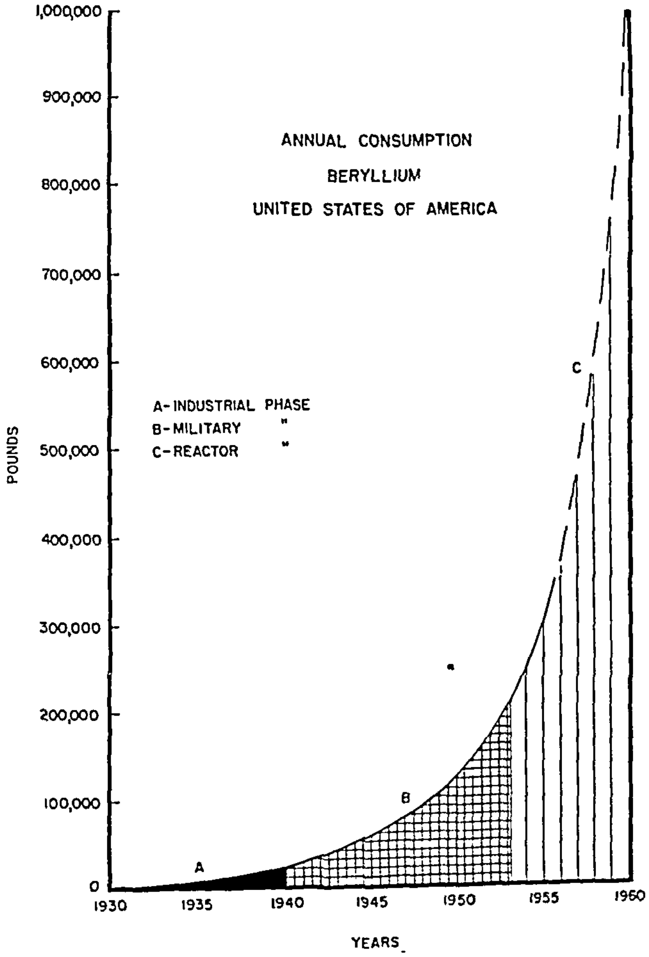

FIGURE 2: The graph illustrates the dramatic increase in the annual consumption of beryllium in the United States. Prior to 1930 less than 100 pounds were used annually. The 10,000 pound level was reached just before the Second World War. From 1939 to 1947 the consumption of beryllium increased from less than 20,000 pounds to more than 100,000 pounds.

which involves the uncontrolled machining or welding of some of these stable element components of the reactor may theoretically lead to the release of a respiratory system hazard. All of these engineering ventures are so new and such excellent precautions have generally been taken to avoid risks, that very little specific information is currently available about health problems. The theoretical possibility remains, however, that at some time in the future some essential precaution may be overlooked. It is just as well, therefore, that the construction, maintenance, and dismantling of reactors be carefully scrutinized for possible sources of health hazards, not only because of the radioactive elements, but also because of the unusual non radioactive substances which are involved.

Basic Biological Effects

To review, in a paper of the present scope, the full range of biological effects provoked by such a diversity of stable elements which may yield respirable hazards, is obviously impracticable. Each inhaled substance can cause lesions of a characteristic type and distribution. However, there are certain broad principles which unify the pathology resulting from exposures to these individual substances. These basic patterns will now be briefly reviewed and illustrated with specific examples.

Pulmonary Lesions:

Being the portal of entry of inhaled particles, fumes, or gases, the respiratory tract naturally requires first consideration. These foreign agents may be arrested at any point in their course to the alveolar membrane, if they are of an insoluble or slowly soluble type. In such instances they often remain embedded in the tissues and then are identifiable by petrographic methods (Figs. 3A and 3B). This is often a great help in differentiating the resultant lesions from disease processes of biological origin. If the etiological agents are readily soluble, they may traverse the pulmonary tissues to become lodged in some other part of the body. In such cases no local clue may be discovered, but appropriate study of distant organs, such as the bones, may continue to furnish the necessary diagnostic information.

Because of the mutiplicity of levels at which the inhaled particles or gases may impinge, the resulting lesions may range from tracheitis, bronchitis, and bronchiolitis to the strictly parenchymal pulmonary reactions. At each of these sites the responses may range from acute and subacute to the chronic in respect of their rate of development. Their grades of severity may be either slight, moderate, advanced, or even fatal. In the area of distribution the responses may be localized, multifocal, diffuse, or universal. With respect to permanence, the lesions may vary markedly. Some are transient, either wholly or partially, while others are irreversible, with or without progression. Qualitatively each lesion may be either exudative, hyperemic or ischemic, catarrhal, necrotizing, degenerative, inflammatory, or proliferative. Cell changes involving abnormal mitosis and ultimately neoplasia may occur. Sometimes several of these types of reaction may be found in the same lung, simultaneously or successively. Phenomena such as sensitization and allergy apply in certain instances. Tolerance may develop in many cases. When inhaled simultaneously or successively, some substances act synergistically and produce a result of which neither component is separately capable. In other instances two agents may behave antagonistically and nullify the action of either one or of both. In a great many instances, too, the inhaled substances appear to have no local effect on the tissues of the respiratory system or evoke a negligible phagocytic defensive reaction only. Theoretically, too, some of these agents should prove beneficial. Regrettably, there are but few instances of the latter phenomenon.

Dosage plays a great part in determining the pattern of lesions induced by individual nocuous agents. The correlation may, however, be either positive or negative. While some agents have a relatively high threshold, the liminal dose is infinitesimally small in other instances. Rate of exposure similarly serves as a determinant of pathology. Intermittent exposures reduce the reaction in some cases and enhance the response in other instances. In most instances, however, lesions regress on cessation of exposure, *pari passu,* with the elimination of the foreign agent from the tissues. In other instances the pathological processes progress in spite of the removal of the subject from the harmful environment. Not infrequently the tissue response is so retarded as only to manifest itself many years after the irritant substance had been introduced. In yet further instances the very withdrawal of the inhalation hazard is

FIGURE 3A

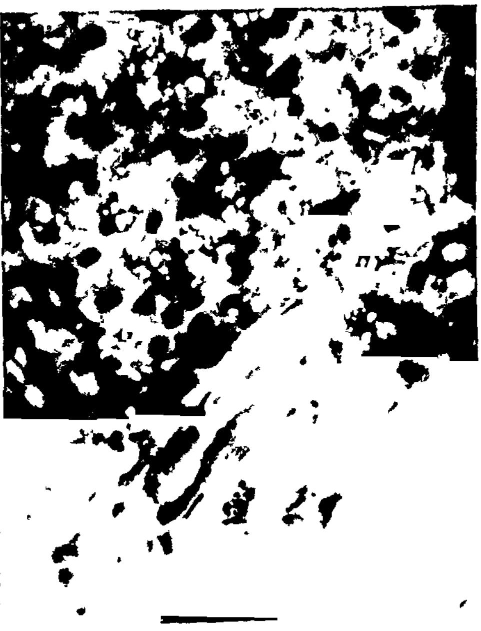

FIGURE 3B

Figure 3A: Opaque mineral particles embedded in the lung tissue of a uranium machinist who developed chronic pulmonary granulomatosis, *confirmed by biopsy* (Hematoxylin *and* Eosin × 800).—*Figure 3B:* Brightly birefringent particles in the lung tissue of a beryllium worker with chronic pulmonary granulomatosis (*Polarized* Light × 800).

promptly followed by a more violent reaction than that observed during the phase of continuous exposure.

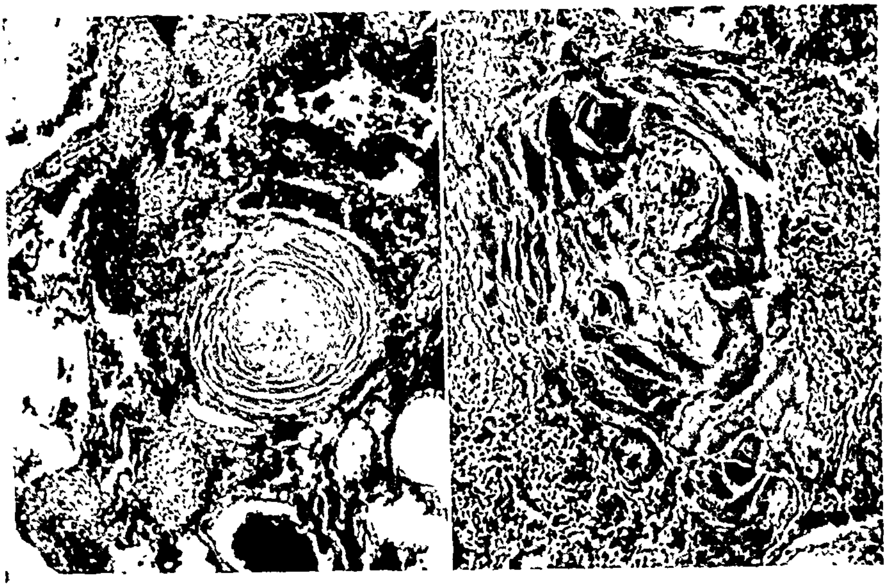
FIGURE 4A FIGURE 4B

Figure 4A: Silicotic type of whorled fibrous nodule in the lung of a beryllium worker with no occupational history of quartz dust exposure (Hematoxylin and Eosin × 65). —*Figure 4B:* Irregular deposit of collagen in a granulomatous zone of the lung of a beryllium worker (Mallory × 175).

Secondary infection frequently plays a significant role in determining the course and outcome in specific syndromes. Tuberculosis is significantly related to the dust exposures in some instances but has no causal relationship in others. The tuberculous process may be enhanced by the pneumoconiosis or may in turn aggravate the latter. Nonspecific infections likewise are either facilitated or suppressed by the concurrent or prior inhalation of nocuous dust particles, fumes or gases. The introduction of the foreign agent may either facilitate the entry of pathogenic bacteria and viruses or may augment the effects of organisms normally resident in the pulmonary tissues.

The foregoing formidable array of possibilities, coupled with the fact that for each element there may be multiple compounds and many physical states in which the nocuous agent can enter the body, plus the ever-present possibility that exposures to many separate substances may occur simultaneously or successively, all help to complicate matters. It is fortunate, therefore, that so many inhaled agents are relatively inert.

The silicotic nodule is still today the hallmark of industrial pulmonary disease. Except in cases where there has been frank exposure to crystalline-free silica, whorled fibrous nodules are unusual occurrences among the group of diseases resulting from exposures to the elements which are of importance to nuclear energy production. Nodules such as these do, however, occur quite inexplicably in circumstances where no silica exposures have been recorded or in the absence of adequate tissue levels of silica (Fig. 4A). More usually focal fibrous deposits assume bizarre shapes and are relatively readily identified as non-silicotic (Fig. 4B).

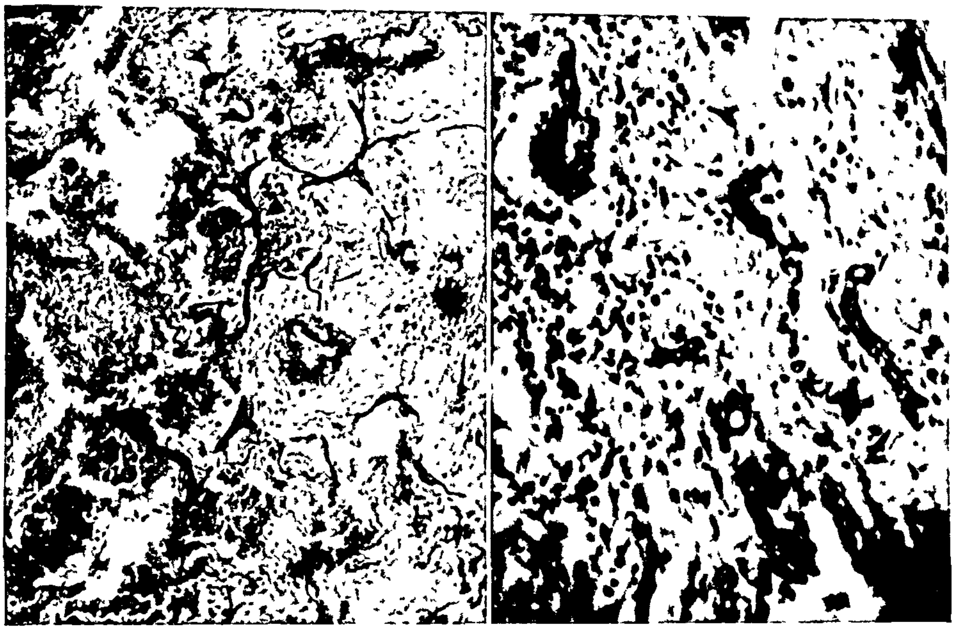

FIGURE 5A FIGURE 5B

Figure 5A: Disruption of the elastic tissue as a delayed manifestation of the inhalation exposure to beryllium (Weigert's × 160).—*Figure 5B:* Mineral impregnated casts of pulmonary capillaries in an area of irregular granulomatous reaction in a beryllium worker (Hematoxylin and Eosin × 350).

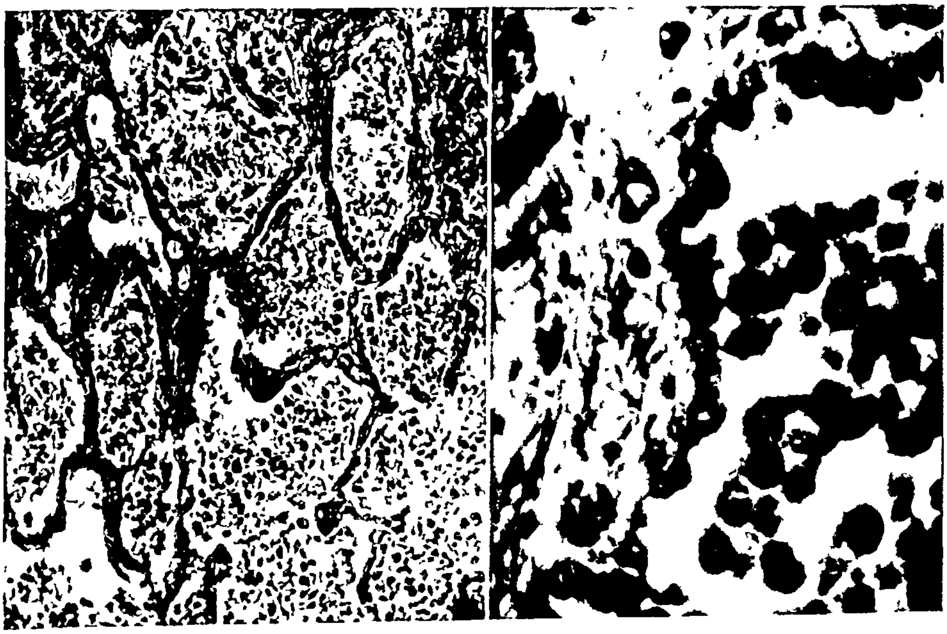

FIGURE 6A FIGURE 6B

Figure 6A: Chronic macrophage catarrh into the alveolar spaces of the lungs of a beryllium worker (Mallory × 190).—*Figure 6B:* Epithelialization of a fibrosed alveolar wall with proliferation of cells into the alveolar spaces of the lungs of a beryllium worker (biopsy) (Mallory × 1000).

The frankly chemical nature of many of the foreign agents of this group often leads to tissue destruction. Such necrobiosis is the basis of several of the varieties of acute chemical pneumonitis. In cases which apparently recover, the results of the acute phase of reaction may persist in the form of destroyed elastic tissue and damaged capillaries (Figs. 5A and 5B). The damage to the pulmonary elastica may be the basis for later emphysema and the relationship may not be identified until a tissue biopsy or autopsy has been performed. Damage to capillaries may be a factor in the subsequent development of cor pulmonale.

While pulmonary cellular catarrh is usually a feature of the early subacute phase, it may persist as a chronic reaction (Fig. 6A). In essence the catarrh represents a constant outpouring of macrophages. There is, however, a further variety of catarrhal response, fortunately rare, in which the discharged cells are of epithelial origin (Fig. 6B). This variety is of more serious import owing to its close approximation to neoplasia.

The best popularized, though not necessarily the most characteristic lesion associated with the inhalation of atomic energy-related stable element particles is the granuloma.[9] This unit lesion assumes many forms but essentially is based on an alveolar membrane and consists of a core of macrophages and giant cells and a surrounding zone of plasma cells supported by reticulum (Fig. 7A). Not infrequently such granulomata are perivascular in location (Fig. 7B). This simply denotes that foreign agent-laden macrophages managed to travel some distance in the pulmonary lymphatic channels before becoming arrested. This result ensues if the foreign agent is less immediately toxic. The ultimate effect, however,

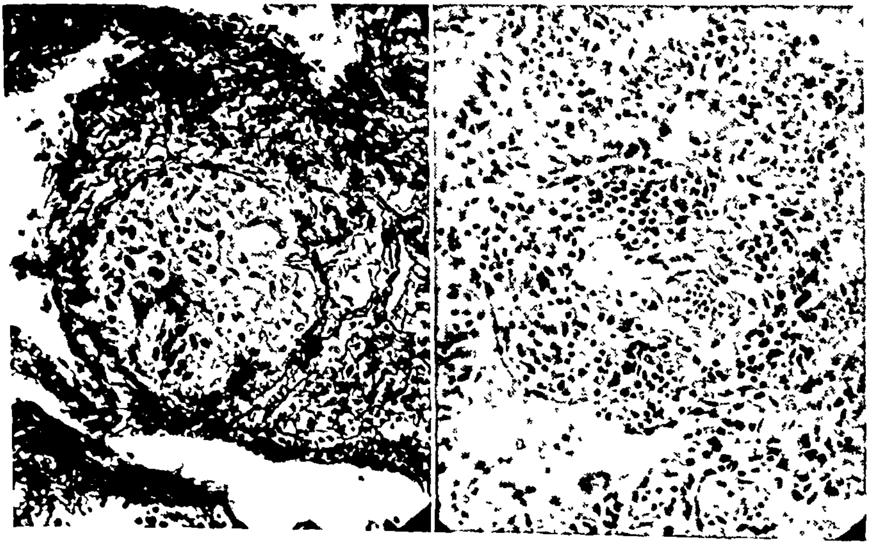

FIGURE 7A

FIGURE 7B

Figure 7A: Alveolar wall granuloma in the lung of a uranium machinist (biopsy) (Foote's Reticulin Stain, × 350).—*Figure 7B:* Perivascular fibrocellular granuloma in the lung of a beryllium worker (Hematoxylin and Eosin, × 300).

may be more disastrous, for occlusion of the affected blood vessel is likely to induce greater disability than would follow the focal loss of alveolar membrane function.

The granulomata have been further characterized through the possession of inclusion bodies of several varieties. The origin of the crystals (Fig. 8A) which are often found in these cases is not clear. Conchoidal bodies (Fig. 8B) have been regarded as separate entities. They probably are excretion products of giant cells. It has been noted that these interesting structures are prevalent in persons exposed to certain groups of elements and less common in other workers exposed to different types of nocuous agents. This may have diagnostic significance but we require more data in order to be sure.

Sequelae:

Among the more obvious local sequelae of the respiratory tract reaction to the inhalation of various stable elements used in the generation of nuclear energy is involvement of the pulmonary adnexae. Earlier experiences with asbestosis and silicosis have focused attention on the exaggerated pleural damage in the former and the far-ranging lymphoid tissue involvement in the latter disease. It is interesting, therefore, to find that the substances which have recently become so important, may behave in this fashion too, though they do not necessarily reproduce identical patterns. In isolated instances, however, the pulmonary adnexae become diseased without the development of a prior or concomitant re-

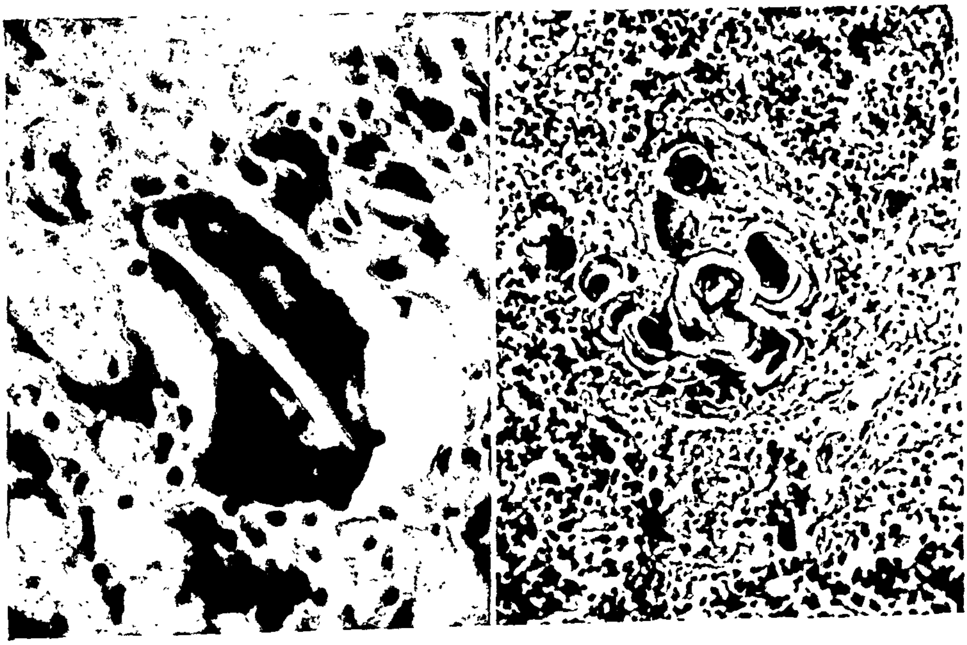

FIGURE 8A FIGURE 8B

Figure 8A: Crystal cleft within a multinucleated giant cell in a beryllium worker with pulmonary granulomatosis (Hematoxylin and Eosin, × 800).—*Figure 8B:* Conchoidal body in a granulomatous area of the lung of a beryllium worker (Hematoxylin and Eosin, × 300).

action in the lungs or air passages. In some cases there can be advanced pulmonary disease without spread to the regional lymph nodes or pleura.

Cor pulmonale constitutes another serious but immediate sequel to the pulmonary disease caused by the group of inhaled substances relevant to atomic energy programs. In the majority of cases the pulmonary hypertension arises directly as a result of the progressive occlusion of capillaries and small blood vessels. This effect is produced by any of the classical mechanisms underlying the development of primary cor pulmonale,[11] but emphasis appears to be placed on the destruction of the pulmonary capillary bed by vascular necrosis (Fig. 9A) and pericapillary fibrosis (Fig. 9B). The relationship between the pericapillary reaction and inhaled particulate matter often is immediately apparent. Occlusion of small blood vessels through endarteritis obliterans is a not uncommon occurrence (Figs. 10A and 10B). Blood vessels may also be narrowed by perivascular cell infiltrations and adventitial cicatricial stenosis. Right ventricular enlargement and strain also undoubtedly result physiologically through chronic hypoxia originating in granulomatous lesions of the alveolar walls and in the emphysema which so commonly is associated with metallic inhalation hazards.

Practically all the lesions observed in human subjects have been reproduced experimentally. The characteristic granulomata of beryllium disease and the proliferation of alveolar wall epithelium have been particularly well reproduced. A much more ominous sequel, not yet proved in man but quite readily producible in rats by means of various beryllium compounds, is neoplasia.[10]

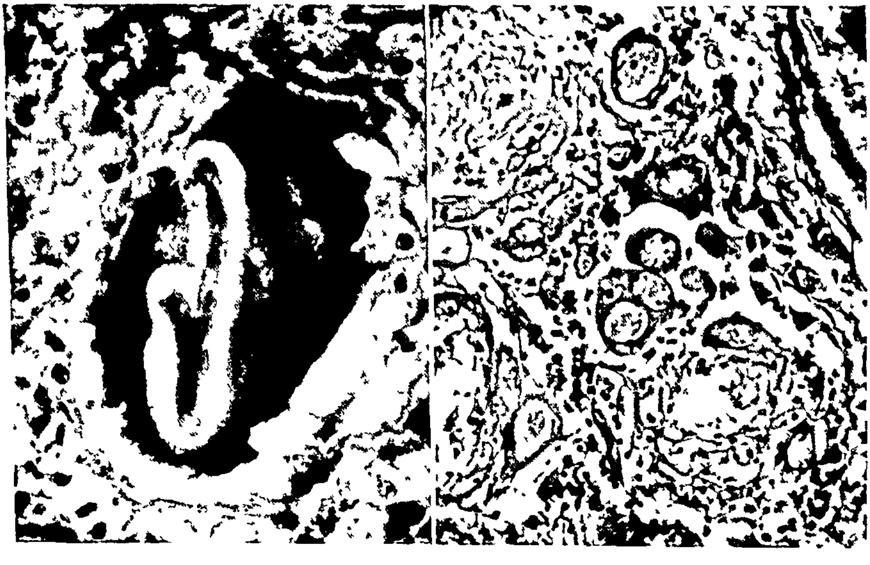

FIGURE 9A FIGURE 9B

Figure 9A: Remnant of a necrosed small blood vessel phagocytosed by a multinucleated giant cell in the lung of a beryllium worker who died of cor pulmonale (Hematoxylin and Eosin, × 800).—*Figure 9B:* Pericapillary fibrosis in the lungs of a beryllium worker who died of cor pulmonale (Mallory, × 350).

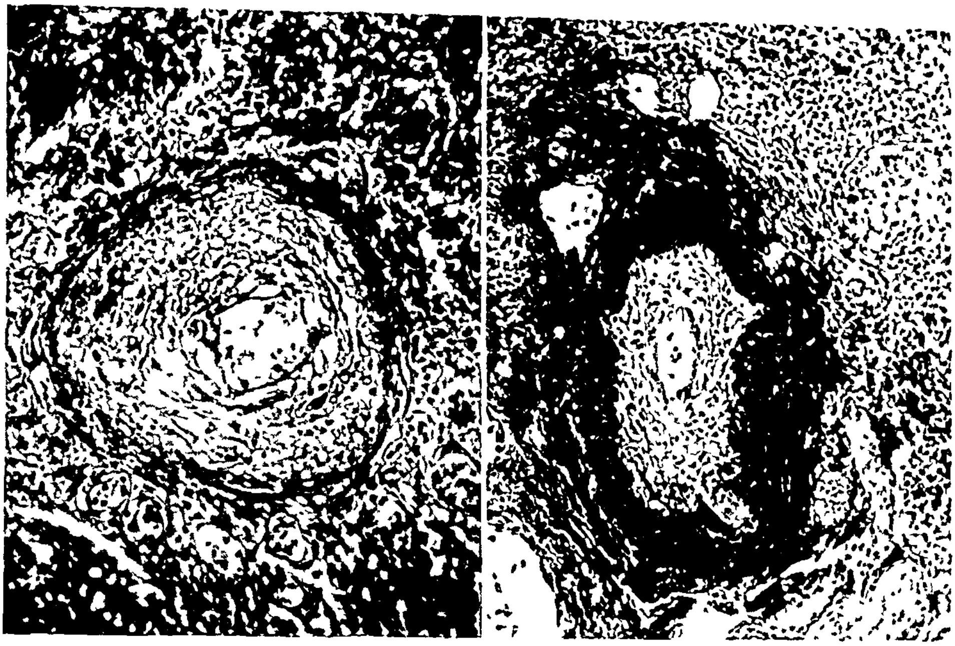

FIGURE 10A

FIGURE 10B

Figure 10A: Endarteritis obliterans of a small blood vessel in a granulomatous area of the lung of a beryllium worker who died of cor pulmonale (Mallory, × 320).—*Figure 10B:* Perivascular cell infiltration and endarteritis obliterans of a medium-sized artery in the lung of a beryllium worker who died of cor pulmonale (Weigert, × 175).

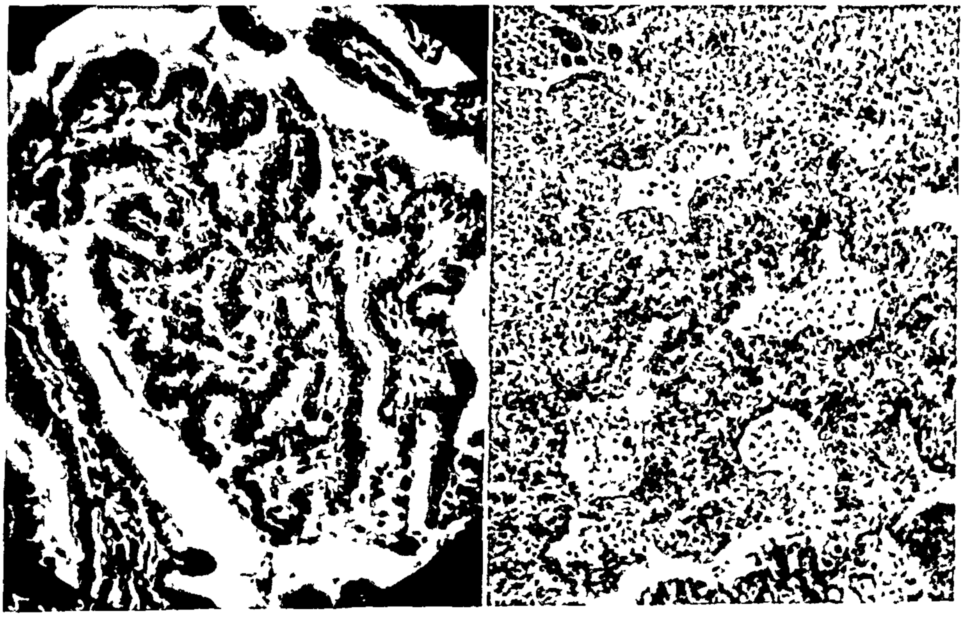

FIGURE 11A

FIGURE 11B

Figure 11A: Pulmonary papillary adenocarcinoma which metastasized to other organs of a rat exposed by inhalation to an aerosol of beryllium sulphate for 6 months and then allowed to reside in normal air for 10 months until killed (Hematoxylin and Eosin, × 300).—*Figure 11B:* Squamous carcinoma in the lung of a rat exposed by inhalation to an aerosol of beryllium sulphate for 6 months and then allowed to reside in normal air for 10 months until killed (Hematoxylin and Eosin, × 175).

Characteristic features of these pulmonary tumors are their great prevalence, their multifocal origin, their pleomorphism (Figs. 11A and 11B), malignancy, and their origin in peribronchiolar alveolar membranes rather than the bronchial mucosa. Astonishing discoveries concern the exceedingly minute doses which can effectively induce neoplasia and the great interval which may elapse between the period of exposure and the inception of the new growth. Frequently no traces of the original chemical irritant are demonstrable in the lung tissue by the time the cancer has formed.

Complications:

As a result of inhalation exposures to various of the stable elements used in atomic energy programs, lesions may be provoked in more remote structures of the body. The capacity of the lung to absorb soluble compounds is stupendous. On being inhaled such substances pass to remote organs with almost the same facility as happens when they are injected intravenously. A fairly large proportion of the compounds of the various elements important to nuclear energy programs are quite soluble. They may, therefore, be rapidly transported from the lungs to organs such as

FIGURE 12: Osteogenic sarcoma which developed in the femur of a rabbit 13 months after it had received 1 gram of zinc manganese beryllium silicate in 20 bi-weekly intravenous injections. Injections of zinc, manganese, and silica separately or combined did not induce sarcomatosis. The total dose of beryllium administered was 29.8 mg.

the liver, kidney, suprarenal, spleen, and bone. Some of the compounds affect these distant organs without even provoking demonstrable pulmonary changes while others also affect the lungs in transit.

Degenerative changes in the liver, kidney and suprarenal result in the obvious metabolic disturbances. Long before dysfunction becomes clinically manifest, however, there may be subtle enzyme and endocrine changes, recognition of which may serve as sensitive indicators of incipient systemic metallic toxemia. Deposition of these chemical agents in bone and bone marrow may have serious consequences. Anemia may be the first result. Polycythemia, on the contrary, may also arise both through local action on the myelopoetic system or as a sequel to the chronic hypoxia due to extensive lung damage. Leukemia is to be anticipated but no proved case has been attributed to stable chemical elements. Bone sarcoma has, however, definitely been produced under experimental conditions.[12] Osteogenic sarcomata were first produced by injections of a fluorescent tube powder containing zinc, manganese, silica, and beryllium (Fig. 12). Subsequently this form of neoplasm was successfully provoked by injections of beryllium oxide only. This occurrence, the more particularly because it is a delayed phenomenon, imparts an ominous significance to the passage of elements across the pulmonary barrier. The danger of bone sarcoma from radioactive fall-out is already much under public scrutiny. The possibility of such a complication through exposures to some of the non-radioactive elements used in nuclear energy programs should not be overlooked.

Discussion

Precise knowledge of the nature of the biological response to the various elements to which men may become exposed in the process of developing atomic energy cannot be achieved without acquiring a concept of the tolerances permissible to the human system. Our understanding of the nature of the disease which may result from such exposures, limited as it is, has far outstripped our information on threshold values. This stricture applies with equal force to almost every phase of the problem. Vast sums have already been spent on research, particularly as it pertains to uranium and beryllium. While many fundamental truths have been uncovered, our knowledge is far from precise. The comprehensive investigations on the toxicity of uranium, sponsored by the Atomic Energy Commission, were limited by the crash program nature of the study enforced by the military emergency. Much was discovered about the effects of acute and subacute exposures to uranium ores and uranium compounds. The influence of long-term exposures and the deferred effects of transient inhalation of uranium compounds still have to be worked out. Many answers will be furnished by the close supervision of uranium miners and plant personnel which already has been instituted in many quarters. Without further experimental research, however, the possibility remains that human beings will serve as the experimental subjects whereas rats and guinea pigs could furnish the answers to extant problems.

The uranium phase of the atomic energy program is probably likely to constitute the lesser hazard for the reason that processing and use of the element is under such direct supervision of competent scientists. It is more probable that other elements may receive insufficient attention. Beryllium may serve as a typical example. Enthusiasms for research on the biological action of this crucial element seem to be waning. Facile assumptions are current that we have all the answers, that the metal and its compounds are under adequate engineering control, and that many of the claims about the toxicity of the substance are spurious and exaggerated. There seem to be more experts on this subject who have never seen a case of beryllium poisoning or who have never conducted an experiment, than there are true connoisseurs. Those of us who have inquired into the problem first-hand are impressed with the paucity of our facts, the magnitude of the enigma and the urgency of the need for precise information. The fact that a million pounds of beryllium metal may soon be available for the construction of nuclear reactors focuses attention on the need for exact information on health hazards. Exposures are unlikely in newer manufacturing plants where serious efforts at health protection have been instituted. Danger of exposure is more probable at the points of exploitation of the metal. We have proved, for instance, that beryllium fluoride, in a dose as low as 1.36 gamma per cubic foot of air (equal to 0.26 gamma beryllium) is a very effective pulmonary carcinogen in rats. While the temptation may exist to assume that the effective dose for man will have to be proportionate to his greater body weight, it should be recognized that each pulmonary cancer may have its origin in but a single vulnerable cell. We have no precise way of knowing whether a human lung cell will need more or less beryllium exposure, to evoke a latent neoplastic tendency, than will a rat lung cell. Perhaps an exposure to beryllium at a level of 0.26 gamma per cubic foot will be just as dangerous for man as it is for the rat. Only further research will help furnish the answer. In the meanwhile, it may be pointed out that a dose of 0.26 gamma beryllium per cubic foot is really infinitesimally small. A single pound of the million pounds of beryllium metal soon to be in use, can produce a concentration of 0.26 gamma per cubic foot in a zone 100 feet deep over an area of approximately 1 square mile!

Diagnosis of an industrial disease is usually facilitated by an exact occupational history. For reasons of security it is possible that potential victims of inhalation exposures to nonradioactive elements may fail to disclose to their physicians significant phases of their work record. This matter would not be mentioned here if it had not already occurred. The common enemies with which we are confronted are disease, disability, death, and genetic decay. Secrecy about symptoms and exposure will help these foes. Every physician should become fully conversant with the precise health implications of current nuclear energy programs. The widely publicized pronouncements of well-meaning veteran physicians, who may be very ill-informed about technical details, do little good and may cause needless panic. More effective control over health hazards will result from the proper instruction of all physicians. Atomic energy problems which once were limited to Oak Ridge or Los Alamos will soon be an issue in scores of cities, large and small. Thus far ignorance about the problem has been understandable. Ignorance in the future will be inexcusable.

The introduction of new elements to which human beings may be occupationally exposed has set a premium on new diagnostic standards. The aim should be to recognize each case so early that construction, maintenance, military, and hygiene engineers can be immediately alerted to the fact that their efforts to eliminate a hazard which has been overlooked should be redoubled. This is the ideal. We may as yet be far from attaining such perfection. Recognition of the clinical forms of these occupational diseases is important, but it essentially comes too late in those instances where a long period intervenes between the phase of effective exposure and the first clinical manifestation of ill health. New laboratory methods, perhaps chiefly those in the domain of enzyme chemistry, may furnish the earliest clues.

Several medico-legal questions are pertinent. Current statutes of limitation debar from just compensation many victims of the deferred sequelae of these occupational diseases. Responsibility for the so-called "neighborhood cases" has not yet been adequately settled. In view of the national importance of the whole program of nuclear energy production, it is patently unjust to continue to permit individual companies to shoulder the full burden of culpability, when all citizens are the beneficiaries of the collective venture. Alarmism and ignorance has probably promoted fraudulent and frivolous compensation claims and consequently seem to have stiffened the defense of some corporations to the point of unreasonableness. Cases which should have been settled out of court have been exposed to the full gamut of legalistic dialectics. Juries, whose minds are repeatedly inflamed by a barrage of sensationalistic publications or who may be swayed by political adherences, hardly constitute the proper tribunals to adjudicate on problems about which the scientists are still so grievously ignorant!

No progress will be made without unremitting research on these multitudinous questions. The scope of disease should be explored in experimental animals of appropriate species and over sufficiently long periods in order to anticipate the occurrence of any of these problems and by effective action to eliminate the hazard before it becomes material. Hygiene standards obviously should be revised, now that we are aware of the fact that several of the newer elements to which man may be exposed behave like trace elements and are effective in extremely minute quantities. Almost nothing is known about antidotes and therapeutic agents. It is sheer pessimism to assume that once a workman has been exposed to a significant dose of carcinogenic beryllium nothing more can be done for him. We already know, for instance, that aurin-tri-carboxylic acid readily combines with various beryllium compounds. This may not be the antidote, but without further research on substances such as this, no prophylactic or therapeutic agent is likely to be discovered.

SUMMARY

1. The military and peacetime nuclear energy programs have greatly expanded the potential scope of human exposures to new and old dust, fume, and gaseous environmental hazards. A large proportion of these new dangers may originate in the biological action of stable elements rather than radioactivity.

2. Exposures are possible in the operations of assembling raw materials, during the processes of extracting, refining, and chemically modifying the various key elements, and in the manufacture of thermonuclear weapons and peacetime reactors.

3. Among the various stable elements, to which exposures are likely, beryllium has the worst record as an inhalation hazard, and this is unfortunate as its strategic nature has greatly increased its use. While some of the newly introduced elements are highly dangerous, a gratifying number appear to be entirely inert. Many of the lesions which may occur in exposed personnel undergo spontaneous remission.

4. Practically all hazards should be preventable by appropriate engineering methods.

5. Various characteristic pulmonary lesions are discussed. Among these the local accumulation of foreign particles, focal fibrosis, cellular and stromal necrosis, chronic macrophage catarrh, epithelialization of alveolar walls, granuloma formation, and vascular damage are the most spectacular.

6. Many of the lesions observed in man have been experimentally reproduced. It has also been possible to induce pulmonary cancer in rats through exposures to various compounds of beryllium even at very low dosage levels.

7. Problems still to be solved, besides methodical, experimental and clinical exploration of the full range of substances to which human beings may be exposed, are: threshold levels of toxicity, especially in connection with prolonged exposures; differential responses in animal species and their applicability to man; precise diagnostic criteria, particularly in life; medico-legal difficulties created by the delayed occurrence of disease after exposure and the national importance of the nuclear energy program; antidotal and therapeutic agents. Only further research can furnish the necessary answers.

RESUMEN

1. Las obras de energía nuclear de tipo militar o pacífico han acrecentado el alcance de las exposiciones humanas a polvos nuevos o viejos, humos, y a riesgos ambientales gaseosos.

Una gran proporción de estos nuevos peligros pueden originarse en la acción biológica de elementos estables más bien que a la radioactividad.

2. Durante el ensamblado de materias primas es posible que haya exposición, así como durante los procesos de extracción, refinación y modificación química de varios elementos esenciales y en la manufactura de armas termonucleares o en la de reactores para fines pacíficos.

3. En los diversos elementos estables a los que es posible exponerse, el berilio tiene el peor record como riesgo de inhalación y esto es muy infortunado porque su naturaleza estratégica ha aumentado mucho su uso. Si bien algunos de los elementos nuevos son altamente peligrosos, un número satisfactorio de ellos parece ser completamente inerte. Muchas de las lesiones que pueden sufrir el personal expuesto, puede tener regresión espontánea.

4. Prácticamente todos los riesgos deben ser prevenibles por métodos de ingeniería adecuados.

5. Se discuten los aspectos de varias lesiones pulmonares. Entre ellas la acumulación local de partículas extrañas, fibrosis local, necrosis celular y del stroma, el catarro macrofágico crónico, la epitelización de las paredes alveolares, la formación de granuloma y el daño vascular, son de las más impresionantes.

6. Pueden reproducirse experimentalmente muchas de las lesiones observadas en el hombre. También se ha podido producir cáncer primitivo en las ratas por medio de exposición a varios compuestos de berilio aún a muy baja dosificación.

7. Hay problemas aún por resolver aparte de los que dependen del método, de la exploración experimental y clínica de todas las substancias a las que se pueden exponer los humanos; tales son: Umbrales de toxicidad, especialmente en relación con largas exposiciones; respuestas diferentes en las especies animales y su aplicabilidad al hombre; criterio diagnóstico preciso, especialmente durante la vida; dificultades médico-legales creadas por el acaecimiento de enfermedad tardíamente después de la exposición y la importancia nacional de los proyectos de energía nuclear; los agentes terapéuticos y los antídotos. Sólo la investigación ulterior puede dar las respuestas necesarias.

ZUSAMMENFASSUNG

1. Die militärische und zivilen Kernenergieprogramme haben die potentielle Reichweite der Exposition des Menschen gegenüber den Umweltzufällen an neuem und alten Staub, Rauch und Gas beträchtlich ausgedennt. Ein grosser Anteil dieser neuen Gefahren hat möglicherweise seinen Ursprung eher in der biologischen Aktion von stabilen Elementen als in der Radioaktivität.

2. Exposition ist möglich bei den Manipulationen der Sammlung des Rohmaterials, im Verlauf der Prozesse der Extraktion, der Reinigung und chemischen Modifizierung der verschiedenen Schlüsselelemente, sowie während der Handhabung der thermonuklearen Waffen und der Zivilen Reaktoren.

3. Aus der Reihe der verschiedenen stabilen Elemente, denen gegenüber eine Exposition wahrscheinlich ist, hat des Benylium das schlechteste Zeugnis als ein zufällig zu inhalierender Stoff, und nun liegt dies unglücklicherweise gerade so, dass jetzt dank seiner strategischen Natur seine Verwendung stark zugenommen hat. Während einige von den neueingeführten Elementen sehr gefährlich sind, scheint eine erfreuliche

Anzahl gänzlich unwirksam zu sein. Viele der Laesionen, die bei gefährdetem Personal eintreten können, unterliegen einer spontanen Remission.

4. Praktisch alle Zwischenfälle müssen sich verhüten lassen durch geeignete maschinelle Methoden.

5. Verschiedene charakteristische pulmonale Laesionen werden besprochen. Unter ihnen sind am auffälligsten die lokale Ansammlung von Fremdkörpern, die fokale Fibrose, die Nekrose der Zellen und des Grundgewebes, chronischer Makrophagen-Katarrh, Epithelialisierung der Alveolarwände, Granulombildung und Gefässschädigung.

6. Viele der beim Menschen beobachteten Veränderungen sind im Experiment ebenfalls erzeugt worden. Es war auch möglich, bei Ratten Lungenkrabs zu erzeugen durch Exposition mit verschiedenen Berrylliumverbindungen selbst in sehr niedriger Dosierungsstufe.

7. Abgesehen von methodischer, experimenteller und klinischer Erforscung der vollen Wirkungsbereiche von Substanzen, denen der Mensch ausgesetzt sein kann, bleibt an Problemen noch zu lösen: die Schwellenwerte der Toxizität, besonders in Verbindung mit langer Exposition; die verschiedennen Reaktionen bei Tierarten und ihre Anwendbarkeit beim Menschen; präzise diagnostische Kriterien, besonders zu Lebzeiten; Gesundheitsgesetzgeberische Schwierigkeiten, die entstehen durch das verzögerte Auftreten der Erkrankung nach der Exposition und die nationale Bedeutung des Kernenergieprogrammes; Gegengifte und therapeutische Stoffe. Allein die weitere Forschung kann uns mit den notwendigen Antworten versehen.

REFERENCES

1 Schepers, G. W. H.: "Ocupational Chest Diseases in Gold Miners," *A.M.A. Arch. Indust. Health,* 12:33, 1955.

2 Schepers, G. W. H.: *The Pulmonary Disability Legislation of South Africa.* Idem—pg. 147.

3 Hueper, W. C.: *Occupational Tumors and Allied Diseases.* Charles C Thomas, Springfield, Ill., 1942.

4 Vorwald, A. J. and Karr, J. W.: "Pneumoconiosis and Pulmonary Carcinoma," *Am. J. Path.,* 14:49, 1938.

5 *Report of the Silicosis Medical Bureau.* U. G. 64:1-57, 1949. Government Printer, Cape Town, Union of South Africa, 1950.

6 Schepers, G. W. H.: *Residual Problems Relating to the Pneumoconioses.* Trans. McIntyre Foundation, 1957. (In press.)

7 Voegtlin, C. and Hodge, H. C.: *Pharmacology and Toxicology of Uranium Compounds.* National Nuclear Energy Series, Div. VI, Vol. I. McGraw-Hill Book Co., Inc., New York, N. Y., 1949.

8 Vorwald, A. J.: Editor, *Sixth Saranac Symposium, Pneumoconiosis— Beryllium, Bauxite Fumes, Compensation,* Sept. 29-Oct. 3, 1947, Leroy U. Gardner Memorial Volume. Paul B. Hoeber, Inc., New York, N. Y., 1950.

9 Schepers, G. W. H.: *Recent Observations on Chronic Pulmonary Disease.* Trans. Twentieth Annual Meeting of Industrial Hygiene Foundation, November 16-17, 1955.

10 Schepers, G. W. H., Durkan, T. M., Delahant, A. B. and Creedon, F. T.: "The Biological Action of Inhaled Beryllium Sulfate: A Pulmonary Chronic Toxicity Study on Rats," *A.M.A. Arch. Indust. Health,* 15:1, 1957.

11 Schepers, G. W. H.: "The Pathology of Cor Pulmonale," *Trans. Am. Coll. of Cardiol.,* 7:48, 1957.

12 Gardner, L. L. and Heslington, H. F.: "Osteosarcoma from Intravenous Beryllium Compounds in Rabbits," *Fed. Proc.,* 5:221, 1946.

The Program of the Atomic Energy Commission for Control of Inhalation Hazards of Nuclear Energy Operations*

H. D. BRUNER, M.D.** and CHARLES L. DUNHAM, M.D.†
Washington, D. C.

Our Atomic Energy Program is one of the truly enormous enterprises of our national life, ranging from mining to computers and heavy industry to oceanography. Consequently, the total number and variety of industrial hazards is potentially large but, fortunately, most of them fall into the category of accepted industrial hazards and require no particular comment. However, when radiation and radioactivity become components of the overall process, each situation and operation must be individually re-evaluated and new industrial standards established as needed. This, of course, is standard procedure at all atomic energy projects, and as a result the AEC has been a partner to a remarkable advance in industrial hygiene and safety engineering techniques. Emphasis has been, and is, on the anticipation of hazards, followed by strict application of preventive measures and education of the worker. In many instances the design and operation of a plant or process has hinged on the recommendation of the health-safety groups. A very welcome by-product of this concern is the enviable industrial record of the AEC contractors.[1]

The lung features very prominently in all thinking and planning concerning possible exposure of personnel to both radioactive and non-radioactive agents. It is recognized as one of the more effective routes for introducing substances inside the body, considering that the alveolar ventilation in an average man amounts to nine kilograms or more of air per day. Whether foreign material in the inspired air will eventually reach the systemic blood depends on its particle size, solubility and some five additional minor properties.[2] In general, by the time the air reaches the larynx, particles larger than about five microns have been removed by the straining action of the vibrissae and by impaction on the moist mucous membranes of the upper respiratory tract; and similarly when the air reaches toward the finer bronchioles, the majority of the particles are one micron in diameter or less; the finest particles have been shown to reach the alveoli. If the larger particles are *insoluble*, they are removed mechanically by ciliary action and coughing. Particles brought up from the tracheobronchial system are for the most part swallowed; if they remain insoluble in the presence of the digestive fluids, their effect is negligible, but if they become soluble or chelated, they may be absorbed into the systemic circulation.[3]

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**Chief, Medical Research Branch Division of Biology and Medicine, U. S. Atomic Energy Commission.

†Director, Division of Biology and Medicine, U. S. Atomic Energy Commission.

On the other hand, if the particles are directly *soluble* in body fluids, the substance can be absorbed through the alveolar membrane *into* the pulmonary capillaries and somewhat less readily across the nasal and bronchial mucosa. Some materials, such as coal, have surface properties which excite phagocytic action; these end up as deposits in the lymph spaces and lymph nodes.

Now where the processes have not involved radioactive materials, modern health-safety procedures and devices have been effective, although some of the compounds used in large amounts definitely are local irritants to the pulmonary tract; others possess toxic effects after having been absorbed into the systemic circulation.

The Atomic Energy Commission's concern with such conventional industrial hazards can be illustrated by the story of nickel carbonyl, $Ni(CO)_4$, a compound used for catalysis and in preparing high purity nickel. It is both a pulmonary irritant and a systemic toxin. Since a vapor can never be fully contained in an industrial process, the operation was designed to maintain a concentration less than the accepted tolerance figure of one part per million. However, because it is a poorly understood chemical toxin, experimental research on the toxicology of the agent was instituted. The data from this project indicate that repeated pulmonary exposures of animals to concentrations of 20 and 40 parts per million lead to a state of chronic irritation of the respiratory tree with evidence of metaplastic changes. The overall findings support the presumed clinical association of this chemical with carcinoma of the respiratory passages,[4, 5] and justify the extra effort needed to maintain the tolerable environmental concentration. A by-product of the study is the development of an effective treatment for systemic nickel poisoning.

Dr. Schepers has described some of the research instituted in connection with the new metallurgical uses of large amounts of stable beryllium. This is typical of the studies on a number of other metals and chemicals, since we are turning more and more to the use of esoteric metals, alloys and chemicals for fabrication of the various types of reactors and their associated machines.

However, when radioactivity becomes a major component of the industrial hazard, every step of each process throughout the entire sequence must be re-examined and re-evaluated. Prior to 1942 the sum of our knowledge of radiation in relation to the industrial population was: 1) that radiation in sufficient amounts was tissue-destructive; 2) that the natural radioactive isotopes such as Ra^{226} could produce neoplasms in areas adjacent to where they localized in the body;[6] and 3) a strong suspicion that men who mined radioactive material had a higher than usual incidence of lung cancer.[7]

Many of the probable sources of radiation and radioactive contamination in the Manhattan Project were easily predicted, but many could not be; therefore, it is to the credit of the Project's medical group and engineers that they designed all operations for maximum anti-radiation protection. This philosophy still is a primary guide line. Nevertheless, there was and is inherent in all atomic energy activities an element of possible exposure to external and internal sources of radiation. Some which are of current interest will be considered.

Much of the uranium ore in the United States is found in relatively circumscribed deposits in the arid Colorado Plateau and as a consequence, the working conditions inside the mines sometimes are less than optimal.[8] Concentrations of radon^{222} or radium emanation, a daughter product of the radioactive decay of uranium, may reach concentrations as high as 6 x 10^{-8} curies/liter of air with averages around 4 x 10^{-9} curies/liter; the acceptable value of 3 x 10^{-10} curies/liter can be achieved in most mines, and proper ventilation of enclosed spaces such as laboratories or machine shops will keep the concentration of Rn to at least 10^{-11} curies/liter, the permissible concentration recommended by the N.C.R.P.[9] A small fraction of this inspired radon gas will be absorbed into the tissues and before being exhaled, it will transform via its decay chain into Pb^{210}, which will then deposit in the bone to exert the effects typical of radium. Other radon molecules will attach to whatever dust particles are present; these then behave like a radioactive form of that dust.

Uranium ore dusts are regarded like other relatively insoluble dusts except that limits of concentration in air have been established which are lower than those for simple silica dust atmospheres. The ore particle may have sufficient radioactivity to impress an appreciable radiation dosage on the underlying bronchotracheal mucosa as the particles are moved upward by ciliary action. A fraction of the ore dust, however, is soluble and is absorbed ito the blood stream. The uranium ion, in contrast to Ra^{226} or Pb^{210}, tends to localize in the kidney;[10] thus the dosage to this organ ultimately determines the permissible environmental concentration. The occurrence of uranium in the urine is evidence of absorption from the lung, although a reliably useful relationship between the two has not yet been established.[11] And, finally, these mines provide a major silicosis problem, enough in some cases to cause a mine to be closed temporarily.

These same three problems also exist in varying degree in the crushing and concentration operations, but can be and are much better controlled. The mining and processing of thorium as a fuel for "breeder" reactors raises similar problems, but this element may be less hazardous from the industrial standpoint.[12]

These conditions are the object of considerable current research. A cooperative study has been developed between the United States Public Health Service, the State of Utah and the Atomic Energy Commision, which is designed to establish permissible standards for uranium mining techniques and ventilation, and simultaneously to evaluate these factors with respect to the health of the miners. Supporting this is a major continuation of experimental work in several AEC laboratories on the toxicology and radiotoxicity of uranium and thorium in the various forms relative to radium, strontium^{90} and pure external gamma irradiation.

Separation of the uranium isotopes for enriched fuel and the production of fuel elements for reactors now are processes operated on a routine manufacturing basis. Once this fuel begins to undergo fission, the type and design of reactor will largely determine the health hazard relative to the pulmonary portal. In the case of an air-cooled reactor, the inflowing air must be cleaned and dried to avoid neutron activation of dusts and foreign material; the discharged air nevertheless contains traces of active dusts plus radioactive krypton, xenon and argon created by the (n, γ) reaction with the stable nuclei of these noble gases. But by use of large volumes of air mixing in a tall stack, the activity is diluted to very low levels before being discharged. If, however, a fuel element fractures or leaks, the fission product mixes into the coolant air going up the stack. To control this contingency, numerous radioactive sampling devices are set to "scram" the reactor automatically whenever the concentration of radioactivity in the stack or in the environmental air exceeds predetermined, very low limits. Experience with the art of reactor operation now makes such scrams rare, but in any case the most that would happen is the beginning of a discharge of radioactive gases, some volatile radioactive isotopes, chiefly iodine and ruthenium tetraoxide, and the dust-like effluvium of some 50 radioisotopes.[13-16] In reactors using a fluid fuel or a liquid coolant moderator, a power surge would result simply in a dispersion of the radioactive liquid but only within the shell or building enclosing the reactor.

During the chemical processing of spent fuel rods or liquid fuels fission products may get into the lungs. This separation process is highly developed and designed to operate by remote control so that ordinarily the pulmonary hazard is negligible; still there have been a few occasions when the system leaked or the stack became overloaded so that it was necessary to evacuate the immediate premises temporarily; however, in no case has the surrounding off-site countryside been affected. Because relatively large quantities of long-lived fission products are in these spent fuel rods, the Atomic Energy Commission has always insisted on the maximum degree of containment of the fission products; this policy has paid off many times.[17] Nevertheless, it is impossible to achieve absolute containment and workers occasionally may be exposed to small degrees of contamination which enter the body by way of the skin, wounds or abrasions, the gastrointestinal tract and/or the respiratory tract. Of most concern under these circumstance are Pu^{239}, Ru^{106}, I^{131}, Cs^{137}, Sr^{90}, Ba^{140}, and perhaps tritium, or H^3; these radioisotopes enter the respiratory tract as gases, as fine dusts, or as aerosols produced by entrainment in other emitted vapors.[16,18] Certain of these isotopes, Cs^{137}, Sr^{90} and Ru^{106}, are of interest from the standpoint of long-term fallout from the stratosphere which enters the body via the food chain. Conversely, the immediate fallout from a nearby burst could create a dust problem for the lung, but the particles are comparatively large.[19, 20]

Some of the very first fission product from the Manhattan Project was set aside for biological studies, because the problem of contamination of personnel was recognized to be a primary limiting factor in all operations. The late Dr. Joseph Hamilton of the Crocker Laboratory, University of California, set up the screening program which provided the initial information on these new radioisotopes; these data were then used to establish the permissible limits and concentrations. This type of work has expanded to the point that a considerable part of the total effort of the Division of Biology and Medicine of the AEC is directed toward obtaining data which can be used to compute the maximal permissible values found in the National Bureau of Standards Handbook No. 52.[9] This handbook, incidentally, will soon be revised using recently accumulated data including an appreciable amount on man himself.

The containment and disposal of radioactive wastes should never create problems relative to the lung because it is under engineering control.[18, 21] However, if a container were to leak or break during transportation to a storage area, the spill could become a source of dusts and aerosols.

The chronic effects of penetrating gamma or x-radiation on the lung are to cause fibrosis and perhaps to act as a carcinogen,[22] but because the lung is grouped with the radio-resistant tissues, one ought to find similar but more lethal damage in tissues such as bone marrow occurring before the fibrosis is able to show itself.

The simple passage of a dilute soluble radioactive aerosol or gas across the lung membranes would not be of much significance to the lung unless the lungs were filled with a very high concentration of it. This, however, may be of practical significance now that krypton^{85} and tritium are available in large amounts of very high specific activity. It has been calculated, for instance, that a single deep breath of pure tritium would give a surface dose to the lung tissue of about 4000 rep per second. More dangerous, however, would be the inhalation of the gaseous form of nearly pure T_2O: In the extreme case, a three-second inhalation of gaseous T_2O would result in an integrated total body dose of between 3,000 to 10,000 rep;[23] on the other hand, a continuous concentration of 5×10^{-6} μc of tritium/ml. of air is estimated to result in the tolerance 0.3 rem per week.[24]

Inhalation of an aerosol which is insoluble in the body fluids presents a different hazard. In the case of plutonium oxide, only a small amount dissolves in the blood; this then is deposited rather firmly in the bone. The remainder moves up the respiratory tract and into the gut, as particles with at least two different half-times of removal, one of about six months and one of a few weeks.[25] Pu^{239} emits α-particles as it decays; these α-particles impose a highly concentrated dose of radiation to the underlying tissue so that a narrow streak of dead or damaged mucosa will be left behind as the particle moves upward. There are large numbers of such particles continuously moving up the same course, giving essentially repetitive radiation which may be especially carcinogenic. In any case this continual radiation dose to the mucosa may be ultimately more damaging than that to the alveoli.

Methods of treating persons with internal contamination are most effective for those radioactive isotopes which have the least tendency to localize in tissues and are most soluble. One attempts as quickly as possible to chelate the absorbed isotope and divert it out the excretory routes. To this end, one gram dose of calicum disodium ethylenediaminetetra-acetic acid are injected intravenously once or twice a day for one to four days. In addition, diuretics, renal acidifying agents, and saline cathartics may be used to magnify the excretory activity. For radioisotopes such as As^{74} or Hg^{203}, British antilewisite (dimercaptopropanol) would be preferred to the above EDTA.

In the case of contamination by plutonium, a single dose of zirconium citrate (25 mg. Kg. body weight) is injected intravenously as quickly as possible in order to saturate the surfaces of the body tissues onto which the plutonium ion would localize. Radioisotopes such as those of Na^+, H^+ and I^- can be most effectively eliminated by giving large amounts of the stable isotope combined with diuresis; by this means the stable isotope dilutes the radioactive form, competes more effectively with it for the available metabolic reactions, and finally carries the radioisotope out of the body when the excess ion is excreted as the homeostatic mechanisms come into play.

The insoluble isotope must be removed mechanically. If the contamination is under the surface, the area is excised. Simple debridement is rarely sufficient to remove the radioisotope since less than milligram amounts remaining in a wound may provide a potentially lethal body burden; occasionally amputation may be warranted.

Rinsing the nasal passages and irrigation of the upper respiratory tract should be carried out as quickly as possible. Unfortunately, nothing effective can now be done to promote more rapid clearance of particles from the lung; this is a point for research. If most of the activity were shown to be localized in one lobe of the lung, lobectomy probably would be indicated.

SUMMARY

The Atomic Energy Commission's broad activities bring it into contact with many situations and compounds which affect the lungs. Most of them, fortunately, are familiar industrial problems for which there are acceptable solutions. Superimposing radiation, however, has necessitated major research and development efforts aimed at controlling contamination and the effects of radiation. Up to now, the record indicates we have been reasonably successful and certainly it is one of the few instances of a major industry making a primary effort in health protection without it being obliged to do so because a series of major accidents took place.

RESUMEN

Las amplias actividades de la Comisión de Energía Atómica la llevan al contacto con muchas situaciones y compuestos que afectan los pulmones. Afortunadamente la mayoría son problemas industriales a los que se han familiarizado y para los cuales hay soluciones aceptables.

La radiación reiterada sin embargo, ha necesitado investigación mayor y el desarrollo de esfuerzos encaminados al control de la contaminación y de los efectos de la radiación. Hasta ahora la observación indica que hemos tenido razonable éxito y ciertamente ésta es una de las ocas ocasiones en

que una gran industria hace un esfuerzo desde el principio par proteger la salud sin verse obligada a ello a causa de la ocurrencia de accidentes grandes.

ZUSAMMENFASSUNG

Die umfangreiche Regsamkeit der Atomenergierkommision bringt diese in Kontakt mit vielen Stellen und Verbindungen, die die Lunge betreffen. Die meisten voh ihnen stellen glücklicherweise bekannte Industrielle Probleme dar, für die sie annehmbare Lösungen bedeuten.

Die zusätzliche Bestrahlung hat jedoch grössere Untersuchungen erfordert und die Entwicklung von Bemühungen mit dem Ziel der Beherschung der Abfallstoffe und der Wirkungen der Bestrahlung. Bis jeszt erweisen die Aufzeichnungen, dass wir ziemlich erfolgreich waren, und sicher ist dies eine der wenigen Gelegenheiten, bei denen ein grosser Industriezweig eine primäre Anstrenung unternimmt zum Schutz der Gesundheit, ohne dazu verpflichtet zu sein, weil eine Reihe von grösseren Unfällen erfolgte.

REFERENCES

1 *U. S. Atomic Energy Commission, Seventeenth Semiannual Report*, July-December 1954, U. S. Government Printing Office, January 1955, pp. 63-65.

2 Drinker, P. and Hatch, T.: *Industrial Dust.* McGraw-Hill, New York, 1954, pp. 65-89.

3 Langham, W.: "The Application of Excretion Analyses to the Determination of Body Burden of Radioactive Isotopes," *Brit. J. Radiol.*, Supplement 7, 1957, pp. 95-113.

4 Kincaid, J. F., Strong, J. S. and Sunderman, W. F.: "Nickel Poisoning. I. Experimental Study on the Effects of Acute and Subacute Exposure to Nickel Carbonyl," *A.M.A. Arch. Indust. Hyg. and Occup. Med.*, 8:48, 1953.

5 Sunderman, W. F. and Kincaid, J. F.: "Nickel Poisoning. II. Studies on Patients Suffering from Acute Exposure to Vapors of Nickel Carbonyl," *J.A.M.A.*, 155:889, 1954.

6 Aub, J. C., Evans, R. D., Hempelmann, L. H. and Martland, H. S.: "Late Effects of Internally Deposited Materials in Man," *Medicine*, 31:221, 1952.

7 Pirchan, A. and Sikl, H.: "Cancer of the Lung in Miners of Jachymov (Joachimstal): Report of Cases Observed in 1929-30," *Am. J. Cancer*, 16:681, 1932.

8 Holaday, D. A., Rushing, D. E., Coleman, R. D., Woolrich, P. F., Kusnetz, H. L. and Bale, W. F.: *Control of Radon and its Daughters in Uranium Mines and Calculations on Biologic Effects.* U.S.P.H.S. Report #494, USHEW, U. S. Government Printing Office, Washington, 1957, p. 4.

9 NBS Handbook #52, *Maximum Permissible Amounts of Radioisotopes in the Human Body and Maximum Permissible Concentrations in Air and Water.* U. S. Department of Commerce, Washington; Government Printing Office, March 20, 1953.

10 Hodge, H. C.: "Mechanism of Uranium Poisoning," Paper P/73, Vol. 13, Peaceful Uses of Atomic Energy, United Nations, New York, 1956, pp. 229-232.

11 Neuman, W. F.: "Urinary Uranium as a Measure of Exposure Hazard," *Industrial Med and Surg.*, 19:185, 1950.

12 Albert, R., Klevin, P., Fresco, J., Harley, J., Harris, W. and Eisenbud, M.: "Industrial Hygiene and Medical Survey of a Thorium Refinery," *A.M.A. Arch. Indust. Health*, 11:234, 1955.

13 Thompson, R. C., Parker, H. M. and Kornberg, H. A.: "Validity of Maximal Permissible Standards for Internal Exposure," Paper P/245, Vol. 13, Peaceful Uses of Atomic Energy, United Nations, New York, 1956, pp. 201-204.

14 Fitzgerald, J. J.: *Determination of Radioactive Fallout*, KAPL Report # 1439, Tech. Information Services, U. S. Department of Commerce, Washington, February 9, 1956.

15 Steinberg, E. P. and Glendenin, L. E.: "Survey of Radiochemical Studies of the Fission Process," Paper P/614, Vol. 7, Peaceful Uses of Atomic Energy, United Nations, New York, 1956, pp. 3-14.

16 Parker, H. M.: "Health Problem Associated with the Radiochemical Processing Industry," *A.M.A. Arch. Indust. Health*, 13:455, 1956.

17 Fitzgerald, J. J.: *Reactor Safeguards*, Handbook of Dangerous Materials, Reinhold Publishing Corp., Ed. 2, New York, 1956.

18 Wolman, A. and Gorman, A. E.: "The Management and Disposal of Radioactive Wastes," Paper P/310, Vol. 9, Peaceful Uses of Atomic Energy, United Nations, New York 1956, pp. 9-16.

19 Miyake, Y.: "On the Distribution of Radioactivity in the North Pacific Ocean," Paper P/1057, Vol. 13, 1954-1955, Peaceful Uses of Atomic Energy, United Nations, New York, 1956, pp. 381-384.

20 Cronkite, E. P., Bond, V. P. and Dunham, C. L.: *Some Effects of Ionizing Radiation on Human Beings*, T.I.D. 5358, U. S. Government Printing Office, Washington, 1956.

21 Wolman, A. and Gorman, A. E.: "The Management and Disposal of Radioactive Wastes," Paper P/310, Vol. 9, Peaceful Uses of Atomic Energy, United Nations, New York, 1956, pp. 9-16.

22 Rhoades, R. P., Chapter 15: *The Lung*. In Histopathology of Irradiation, Editor: W. Bloom, National Nuclear Energy Series IV-221, McGraw-Hill, New York, 1948, pp. 704-711.

23 Anderson, E. C. and Langham, W. H.: *A Theoretical Consideration of the Hazards Associated with Acute Exposure to High Concentration of Tritium Gas*, LASL Report 1646, Los Alamos, N. M., February 1954.

24 Pinson, E. A. and Langham, W. H.: "Physiology and Toxicology of Tritium in Man," *J. Appl. Physiol.*, 10:108, 1957.

25 Wager, R. L., Dockum, N. L., Temple, C. A. and Willard, D. H.: Toxicity of Radioactive Particles, 1-A. Intratracheal Injection of Radioactive Suspensions, Yearly Progress Report for 1955, General Electric Company, Hanford, Washington, H. W. 41500, pp. 61-72.

The Public Health Aspect of Nuclear Energy, With Particular Reference to Inhalation Hazards and to Diseases of the Chest*

ALBERT L. CHAPMAN, M.D.**
Washington, D. C.

"The public health aspect of nuclear energy" is, without doubt, the most formidable phrase that any medical man was ever requested to include in the title of his address. Since a certain summer day 12 years ago the entire population of the globe has stood face to face with the unprecedented problem these words express. Our "public" in this sense includes every human being on earth. The best brains in the world have struggled with the problem for more than a decade and, as the newspapers and magazines assure us with ever increasing stridency, have reached no agreement, even on definition of terms.

This, gentlemen, is a discussion topic that even a Washington official finds himself approaching with something less than that occupational self-confidence of which we are, from time to time, accused.

Often, however, a new job turns out, upon examination, to contain familiar elements, and the rather staggering nature of many new assignments begins to cause less apprehension when we discern that many of the components are customary, standard procedures with which we have worked for a long time.

The dawn of the atomic age, and the health hazards inescapably associated with the use of nuclear energy, may appear to present the public health profession with its newest responsibility, but in truth this energy-revolution simply renders more dramatic, and perhaps more urgent, the basic responsibility which is as old as the public health movement—the responsibility for creating and guarding a safe environment in which man can live and in which man can work. Many traditional public health disciplines—I am thinking of sanitary engineering, medical research, and industrial health—have over the years perfected the tools and provided the training for public health workers who must, in the decades ahead, solve the new problems that will grow with each step we take into this atomic age.

Before discussing what the public health profession can do—and is doing—about potential radiation hazards, it may be useful to distinguish, as we do in the field of air pollution, between the acute and chronic effects of exposure. Only where a serious accident occurs, caused by large radiation exposures, can acute effects be anticipated. The symptoms will appear within a few days or weeks and should be immediately recognizable. Chronic low-level radiation exposure is at the present time the more important public health problem (again, there is an analogy with air pollution).

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**Division of Special Health Services, Public Health Service, U. S. Department of Health, Education, and Welfare.

What are the principal sources of radiation exposure?

From the public health point of view the wartime, and subsequent military employment of atomic energy is only one of several sources of total population exposure to radiation.

The testing of bombs, and other developments connected with the military use of atomic energy, have caused international debate over atomic health hazards to reach new heights in recent months; and the interest of the Public Health Service in protection methods in uranium mining was accelerated by wartime activities. There are, however, three chief sources of radiation exposure that constitute the purely civilian aspect of this problem. I have in mind first, the type of exposure which is related to the peacetime atomic energy industry; second, the exposure which results from the presence of natural radioactive substances in the environment and from cosmic rays; and third, exposure encountered in the healing arts, especially in x-ray procedures.

The European project for the international development of atomic power for industry (Euratom) will, it is expected, contribute to the expansion of atomic industry in this country during the next decade, although the American need for a new source of industrial power is far less urgent than the European requirement. Both the workers in the atomic-fueled plants of the future and the general population must be protected from various types of radiation hazard (including the dangers inherent in the disposal of radioactive wastes). Few public health assignments will have a higher priority when we reach the stage where nuclear energy has become a serious rival to coal and oil as a principal support of American industrial strength. The techniques of industrial or occupational health will also at that time be tested to the utmost.

The second source of radiation exposure—radioactive substances in the environment and cosmic rays—is for the most part beyond man's control. We are all exposed to a natural background of radiation, compounded of cosmic radiation (and its secondary radioactivity), the radioactive elements present in the earth (radium and radioactive potassium, for example), and even a minute proportion of certain of the elements present in the human body itself. This natural background is not uniform throughout the world, nor in all parts of this country. At higher altitudes the contribution of cosmic radiation increases, and, of course, there is an uneven distribution of the deposits of radioactive elements in the earth.

The sum total of natural sources of radiation—over which we can exercise little control—is generally regarded by experts at the present time as constituting the second largest single source of radiation exposure with which we are confronted. The largest source is that related to the healing arts. The danger of overexposure of x-ray operators, other medical personnel, and patients themselves is a direct challenge to public health, and a challenge to which we have responded.

The first reported case of human injury from radiation came only a few months after publication of Roentgen's original paper (1895) announcing the discovery of x-rays, and during the following decade many of the now familiar acute and chronic radiation effects were observed and reported.

The principal chronic effects of radiation are understood today to be (1) reduction of the life span, (2) production of genetic mutations, and (3) increased incidence of cancer. For example, an increase in leukemia and other neoplasms, as well as an increase in the number of congenital abnormalities in the offspring of radiologists, as compared with other medical specialists has been reported.

At the present time it is estimated that some 250,000 individuals in this country are engaged in the operation of about 125,000 medical and dental x-ray and fluoroscopic units. This total includes physicians, dentists, veterinarians, nurses, and others.

Since medical and dental uses form the largest single source of radiation exposure, the potential hazard to the patient must *in each individual case* be carefully balanced against the potential life-saving gain that may be realized through the employment of x-rays. The decision in each case must be made, of course, by the individual physician or dentist, since he alone can make a personal evaluation of all pertinent factors in the case.

While the traditional patient-physician relationship is seldom more dramatically justified than under these circumstances, research progress in recent years emphasizes the need for taking into consideration a vital non-personal factor. By this I mean that personal exposures that might have been acceptable in the absence of any other environmental exposure should now be re-evaluated in the light of current knowledge concerning the *total and potential radiation exposure of the entire population from all sources.*

The ultimate responsibility for the establishment and enforcement of uniform radiation health standards remains with State and local health agencies, in accordance with the American tradition of local self-government, but the Federal contribution in this field can be as effective as in other areas of public health.

Broad environmental control activities have been prominent features of the work of the Public Health Service in radiological health thus far, but we are moving into a period of increased emphasis on the medical aspects of control of radiation hazards. Existing training programs developed by the Service to increase the competency of health agency personnel in the environmental field will be supplemented by short courses designed to meet the needs of health agency medical personnel. The accompanying expansion of State and local training programs of a similar nature will be encouraged.

In addition to training, research and the dissemination of information are standard Public Health Service operations. The need for epidemiological research in the quantitative aspects of low-level radiation hazards is an urgent one. Only through epidemiological studies of sizeable populations with known exposure to radiation can we secure the data required for determining maximum permissible exposure levels accurately. At the present time wide variations in exposure are reported, even within the same groups. For example, recent studies have indicated that, among x-ray practitioners, exposure varies from none at all to a figure in excess of the current "permissible" rate.

Techniques are available for reducing the exposure resulting from x-ray and fluoroscopic machines without adversely affecting (and, in some cases, with an actual improvement of) the diagnostic quality of the results. Wider dissemination of information concerning these techniques can be achieved by public health workers in close cooperation with the medical profession. Health officers, engineers, public health nurses, health educators, and other categories of public health personnel can all play a useful role in this cooperative educational effort.

A major activity of the Public Health Service in the special field of inhalation hazards and diseases of the chest has been the work carried on in the uranium mining industry.

The European experience in this connection is important. For 500 years mining operations have been carried on in the Erz Mountains of Czechoslovakia and Bohemia and, after the discovery of radium, pitchblende in these mines was exploited for its radium content. For centuries writers have noted the high mortality from pulmonary diseases among miners in this area, and toward the end of the 19th century investigators identified the affliction as a malignant tumor of the lungs. Some medical reports attributed to primary cancer of the respiratory system as high a proportion as from one-half to three-quarters of all deaths among workers in these mines, and currently the predominant opinion is that radioactivity in the mines has been responsible for the situation.

While it was recognized that European and American mines are in many ways not comparable, it was natural for public health agencies to become seriously concerned over the potential health problem represented by the beginning of uranium production on a large scale in the United States. Although our mines are more shallow than those in the Erz Mountains, and yield a less complex ore, while our miners seldom work underground more than 40 hours a week, still early environmental studies in American uranium mines had revealed considerable concentrations of radioactive gases and dust.

The Public Health Service, therefore, initiated research into the problem of adequate control measures for the mines and undertook, in cooperation with State health departments and the industry, a series of periodic physical examinations of the miners.

What happens in a uranium ore body is that uranium 238 very slowly, and through successive transformations, is converted to radium 226 which, in turn, disintegrates into radon, a radioactive gas about seven times as dense as air. Radon is diffused from the ore and is released by drilling and blasting operations, becoming dispersed throughout the mine atmosphere. Also, within several days, radon itself breaks down into radium A. Radium A and subsequent transmutation products are called radon "daughters."

The daughter products tend to adhere to dust particles, because of their electrostatic charge, and they thus enter the respiratory system in two ways—through inhalation of radon gas and through inhalation of dust particles in the mine atmosphere.

The work of the Public Health Service has demonstrated that, through proper ventilation of uranium mines, the concentration of radon and its daughter products can be reduced to a recommended level, and the lungs of uranium miners can be protected from radioactive gases and dust. Physical examinations of 2,000 uranium miners have been carried out 3 times since 1950, and have been supplemented by an annual census and followup of the miners, in an effort to determine whether there has been health damage to workers in uranium mines in the United States that might be attributed to radiation.

It has been emphasized that the establishment of adequate control measures, such as ventilation, should not be delayed, since by the time biologic damage becomes clinically detectible it may be unresponsive to medical therapy. The latent period for development of lung cancers in European miners was from 10 to 17 years. According to 1956 Census records there are 65 miners with over 10 years of experience in American uranium mines.

The application of industrial health principles, and of occupational health experience such as that gained in work with silicosis over the years, has contributed to the solution of inhalation hazards in uranium mining. It likewise illustrates the applicability, which I mentioned earlier, of traditional public health tools and procedures to this great new health problem area of nuclear energy.

We believe that we have the tools to cope with this problem of exposure of our population to radiation from many sources.

The task ahead is one of organization, research, and application.

SUMMARY

The dawn of the atomic age, and the health hazards inescapably associated with the use of nuclear energy, presents the Public Health Service with its newest responsibility.

We must distinguish in radiation health hazards, as we do in the field of air pollution, between the acute and chronic effects of exposure. Only when an accident occurs, caused by very large radiation exposure can acute effects be anticipated. The symptoms will appear within a short time and should be immediately recognizable.

There are three chief sources of radiation exposure that constitute the purely civilian aspect of this problem. First, the type of exposure that is related to peace-time atomic energy. Second, the exposure which results from the presence of natural radioactive substances in the environment and from cosmic rays. Third, exposure encountered in the healing arts, especially x-ray procedures.

Workers in the atomic-fueled plants of the future, and the general population must be protected from various types of radiation hazards (including the dangers inherent in the disposal of radioactive waste). Radioactive substances in the environment and cosmic rays, are for the most part, beyond man's control. The danger of over-exposure of x-ray operators, other medical personnel and patients themselves is a direct challenge to public health, and a challenge to which we have responded.

The principal chronic effects of radiation are understood today to be reduction of life span, production of genetic mutations, and increased evidence of cancer. At the present time some 250,000 individuals in this country are engaged in the operation of about 125,000 medical and dental x-ray and fluoroscopic units.

Techniques are available for reducing the exposure resulting from x-ray and fluoroscopic machines without adversely affecting the diagnostic quality of the results.

Health officers, engineers, public health nurses, health educators, all play a role in a cooperative educational program.

A major activity of Public Health Service in the special field of inhalation hazards and disease of the chest has been the work carried on in the uranium mining industry. The Service has demonstrated that through proper ventilation of uranium mines, the concentration of radon, and its daughter products can be reduced to recommended levels and the lungs of uranium miners can be protected from radioactive gases and dust.

RESUMEN

La aurora de la edad atómica y los peligros a la salud forzosamente asociados al uso de la energía atómica, presentan a los Servicios de Salubridad Pública nuevas responsabilidades.

Debemos distinguir en los peligros de la radiación para la salud, como lo hacemos en el campo de la polución del aire, entre los efectos agudos y los crónicos de la exposición. Los efectos agudos pueden esperarse sólo cuando ocurre un accidente causado por una gran exposición a la radiación. Los síntomas en este caso aparecerán pronto y deben ser reconocibles inmediatamente.

Hay tres fuentes principales de exposición que constituyen el aspecto civil del problema. Primero: el relacionado con el uso de energía atómica en tiempo de paz. Segundo la exposición resultante de las substancias radioactivas en el medio circundante y, Tercero: la exposición que se encuentra en el arte de curar especialmente por los rayos X.

Los trabajadores en las plantas de combustible atómico del futuro, y la población general, debe protegerse de las varias formas de la radiación (incluyendo los peligros que corresponden a los materiales radioactivos de desecho). Las substancias radioactivas en el medio circundante y los

rayos cósmicos, son en su mayoría incontrolables por el hombre. El peligro de sobre-exposición de los operadores de rayos X, otro personal médico y los mismos enfermos constituyen un desafío a la salubridad pública, un desafío al cual hemos respondido.

Los efectos crónicos de la radiación se comprenden ahora como un acortamiento de la duració de la vida, producción de cambios genéticos y una mayor frecuencia del cáncer. Actualmente alrededor de 250.000 personas este País trabajan en 125.000 unidades de rayos X médicas y dentales.

Existen ténicas para reducir la exposición a los rayos X y a la fluoroscopía sin dañar a la calidad del trabajo.

Los empleados de salubridad, ingenieros, enfermeras de salubridad, educadores sanitarios, todos, desempeñan un papel en el programa educacional cooperativo.

Una actividad importante de los servicios de salubridad pública en el campo de los peligros de la inhalación y enfermedades del pecho se ha desarrollado en la industria de las minas de uranio.

El servicio ha demostrado que por medio de una ventilación adecuada de las minas de uranio, la concentración del radón y de sus productos puede reducirse a los niveles recomendados y los pulmones de los mineros de uranio pueden protegerse de los gases y polvos radioactivos.

ZUSAMMENFASSUNG

Der Anbruch des Atomzeitalters und die unmittelbar mit der Verwendung von Kernenergie verknüpften Gesundheitsschädigungen bescheren dem öffentlichen Gesundheitswesen seine jüngste Verantwortung.

Bei den gesundheitlichen Strahlenschädigungen müssen wir, wie wir es auch auf dem Gebiet der Luftverunreinigung tun, unterscheiden zwischen den akuten und den chronischen Wirkungen der Exposition. Nur wenn ein Unfall eintritt, der durch eine sehr ergebliche Strahlen-Exposition verursacht wird, können akute Wirkungen erwartet werden. Die Symptome werden innerhalb kurzer Zeit erscheinen und müssen unmittelbar erkennbar sein.

Es gibt 3 Hauptquellen der Strahlen-Exposition, die die rein zivile Seite dieses Problems bilden: zum ersten den Typ der Exposition, der verknüpft ist mit der friedlichen Atomenergie. Zum zweiten die Exposition, die sich ergibt aus der Gegenwart von natürlich radioaktiven Substanzen in der Umwelt und von kosmischen Strahlen. Zum dritten die Bestrahlung, der man in der Heilkunde begegnet, vor allen den Röntgenstrahlen.

Es müssen die Arbeiter in den mit Atomkraft betriebenen Werkanlagen der Zukunft und die gesamte Bevölkerung geschützt werden vor den verschiedenen Tspen von Strahlenschädigungen (einschl. der Gefahren, die mit der Beseitigung von radioaktiven Abfällen verknüpft sind). Radioaktive Substanzen in der Umwelt und die kosmischen Strahlen liegen zum grössten Teil jenseits der menschlichen Kontrolle. Die Gefahr der Strahlen-Überdosierung bei den mit Röntgenstrahlen Beschäftigen und anderem medizinischen Personal und bei den Kranken selbst ist ein unmittelbares

Anliegen des offentlichen Gesundheitswesens und ein Anliegen, dem wir entsprochen haben.

Unter den haupsachlichen chronischen Wirkungen der Bestrahlung versteht man heute die Herabsetzung der Lebensdauer, das Entstehen von Gen-Mutationen und das zunehmende Auftreten von Krebs. Im gegenwartigen Zeitpunkt sind ungefahr 250,000 Personen in den Vereinigten Statten beschaftigt mit der Handhabung von etwa 125,000 arztlichen und zahnärztlichen Rontgenaufnahme und Durchleuchtungsgeraten.

Es stehen Methoden zur Verfugung zur Verringerung der Strahlen-Exposition, die bei den Rontgenaufnahme- und Durchleuchtungsgeraten vorkommt, ohne die diagnostischen Qualitaten der Befund ungunstig zu beeinflussen.

Gesundheitspfleger, Techniker, Fursorgerinen, Gesundheitslehrer, sie alle spielen eine Rolle im gemeinschaftlichen Erziehungsprogramm.

Von grosser Wirksamkeit fur das offentliche Gesundheitswesen auf dem besonderen Gebiet der Unfalle durch Inhalation und Thoraxerkrankungen war die in der Uran gewinenden Industrie entfaltete Tatigkeit. Die hier ausgefuhrten Arbeiten haben bewiesen, dass durch entsprechene Beluftung der Urangruben die Konzentration von Radium-Emanation und ihrer Tochterprodukte auf zulassige Hohen herabgesetzt und die Lungen von Uranbergleuten vor radioaktiven Gasen und Staub geschutzt werden konnen.

Early Diagnosis and Treatment of Tuberculosis in Children*

EDNA M. JONES, M.D., F.C.C.P.** and W. L. HOWARD, M.D., F.C.C.P.**
Northville, Michigan

For the early diagnosis of tuberculosis in children, routine tuberculin testing and a careful and detailed history are of prime importance. A careful physical examination should also be done although in the early primary infection it most likely will be entirely negative. Chest x-ray films are not as specific as is the tuberculin test but they are more specific than the symptoms, and they are very important. It is difficult to obtain a definitive x-ray film on a squirming child but it is impossible to make a diagnosis on a poor film. An apparently negative film does not rule out active tuberculosis, especially in the tuberculin-converter with recent heavy tuberculosis exposure. Miliary and meningitis develop in some babies whose films showed little or no evidence of a primary complex. Calcium deposits sometimes appear later in serial x-ray films at the site where only equivocal soft shadows were visible on the first films. After the 9 per cent miliary cases and the 2 per cent reinfection pulmonary cases are excluded the incidence of initial positive gastric cultures among the remaining 89 per cent of the in-sanatorium children is about 27 per cent. Positive gastrics are not uncommonly associated with these equivocal shadows.

The fact that primary tuberculosis lesions may be hidden in the routine x-ray film by the heart, mediastinal structures, large vessels or the diaphragm is well known. Dr. J. A. Myers reports that comparison of antemortem chest films and autopsy findings show that posteroanterior films of the chest fail to reveal 90 to 95 per cent of recent primary lesions and 70 to 90 per cent of long standing primary lesions. Dr. Henry Sweany found at autopsy that 31 per cent of pulmonary lesions were so located that they were obscured in the posteroanterior chest films. In addition 10 to 15 per cent of tuberculosis lesions are extrapulmonary and would, therefore, be missed by the routine chest film. These facts must be kept in mind when evaluating any case from the standpoint of tuberculosis. Histoplasmosis may cause either the primary type or miliary type lesions in the lungs: foreign bodies in a bronchus may cause lesions resembling those of the atelectasis distal to bronchial obstructive types of primary tuberculosis and not infrequently the roentgenologist's report concludes with "please repeat x-ray film in two weeks to rule out pneumonia."

In taking the history one must remember that dates in children are of considerably more importance than in adults; e.g., date of babyhood and of puberty, date of beginning and end of contact with "open" tuberculosis, date of onset and of duration of symptoms, date of negative and of positive tuberculin reaction, date of BCG innoculation (if any) and date of negative and of positive x-ray findings. The effort used in obtaining this information will be fully justified.

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**William H. Maybury Sanatorium.

Since January 1, 1956, 335 children from the Detroit area have been treated in Maybury Sanatorium; 98 per cent of them had a positive tuberculin test and 85 per cent of them had x-ray film evidence of primary tuberculosis in the lungs although 35 per cent of them had other tuberculosis.

A review of these 335 cases shows that almost three-quarters of them had the onset of tuberculosis before five years of age. This certainly indicates that tuberculin testing should be done routinely in well-baby clinics, doctors' offices, and hospitals as part of the examination of all children and not left to the surveys of children of school age.

In detail the age of onset of tuberculosis in the pre-school group was found to be as follows: under one year of age 17.9 per cent, one year 21.8 per cent, two years 15.5 per cent, three years 8.4 per cent, four years 8.9 per cent. The earliest onset was at five weeks of age and she was admitted to the sanatorium at two and one-half months of age in a state of shock. She was drowning in bronchial secretions which were already positive for tubercle bacilli. The fact that a greater proportion of these infected babies will early develop serious and stormy symptoms makes them sensitive and accurate clinical barometers of "open" tuberculosis in the home.

The age of onset was five to eight years inclusive in 21.8 per cent of the children. This would indicate that their resistance to the development of clinical tuberculosis is only slightly less in relation to babies and to pre-

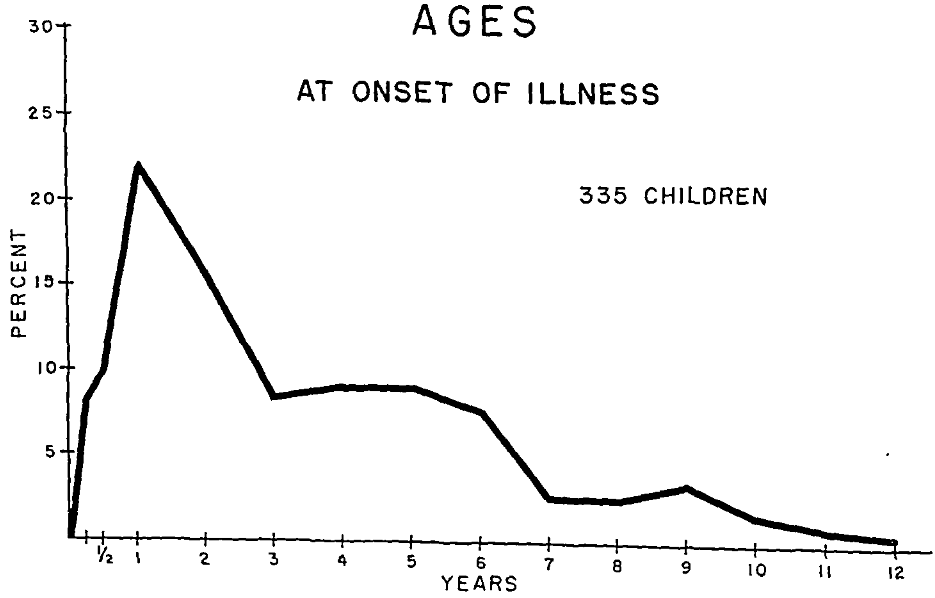

FIGURE 1

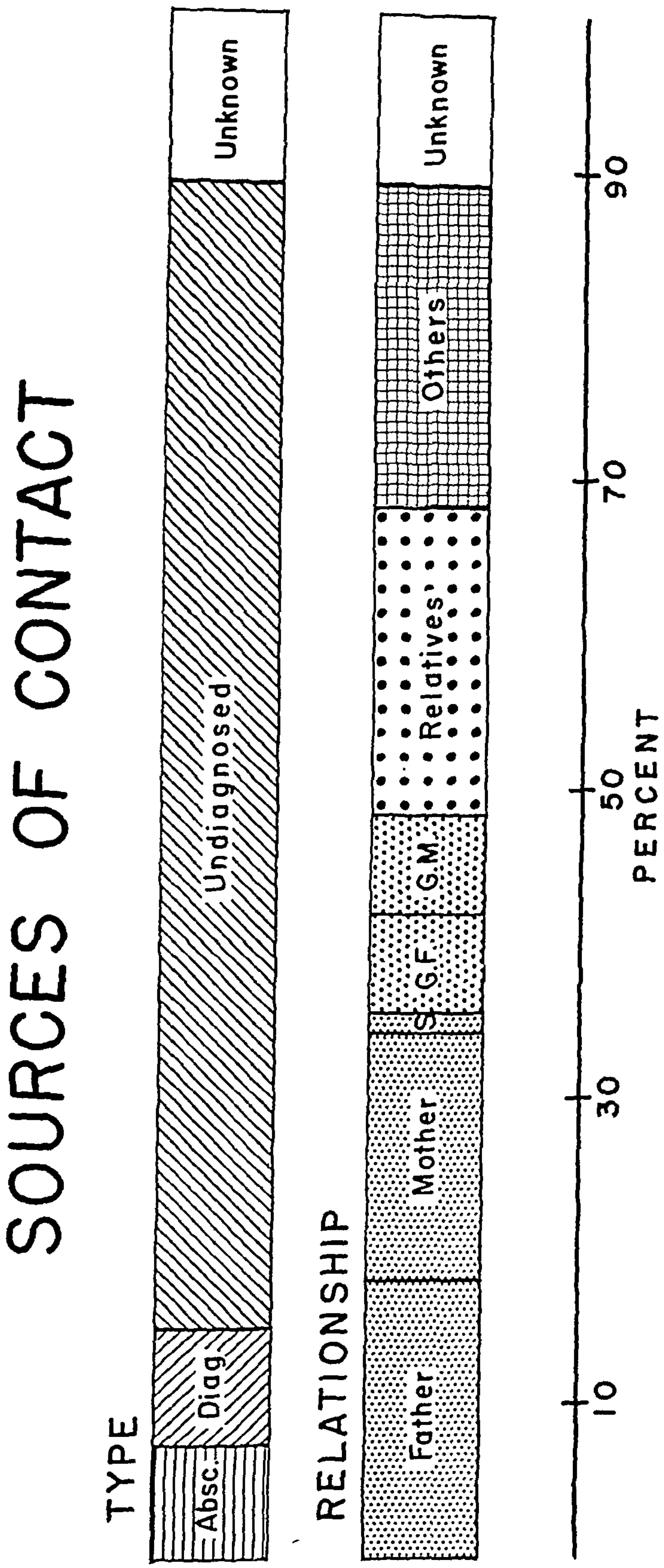
SOURCES OF CONTACT
TYPE
Absc.
Diag.
Undiagnosed
Unknown
RELATIONSHIP
Father
Mother
S
G.F.
G.M.
Relatives
Others
Unknown
10
30
50
70
90
PERCENT

FIGURE 2

adolescents or adolescents and that their age should not preclude the use of specific therapy as soon as fresh active tuberculosis is discovered.

The age of onset was nine to twelve years inclusive in 5.7 per cent of the children. Our upper limit of admission age is the 12th birthday. Over two-thirds of the children having onset at nine to twelve years were pre-adolescent Negro girls; while the remainder were boys who were not yet pre-adolescent and had the same ethnic distribution as the whole population of the Maybury Sanatorium Children's Division, i.e., 40 per cent white and 60 per cent Negro.

Further analysis of these 335 children emphasizes the need for better education, cooperation, and control of the adult with active tuberculosis. When an "open" case of tuberculosis is found, an attempt should be made to estimate the duration of this adult's infectivity. Then a careful history should be obtained as to all the places where and all the persons with whom he lived during that time. It is not enough to check just the present household.

About 74 per cent of the children were infected by adults who had not previously been diagnosed as having tuberculosis: More than 15 per cent were infected by persons who were known to have tuberculosis (7.4 per cent had absconded from sanatoria, 7.8 per cent had had a previous sanatorium admission or an x-ray film diagnosis in a survey unit, selective service, employment, a clinic, or a doctor's office). The source of contact was not found for 11 per cent of the cases.

The source of contact as to immediate family, other relatives, and non-relatives is as follows; roughly 16 per cent of the children were infected by mothers, 18 per cent by fathers, one per cent by siblings, seven per cent by grandmothers, six per cent by grandfathers, eight per cent by aunts, 10 per cent by uncles, two per cent by cousins and 21 per cent

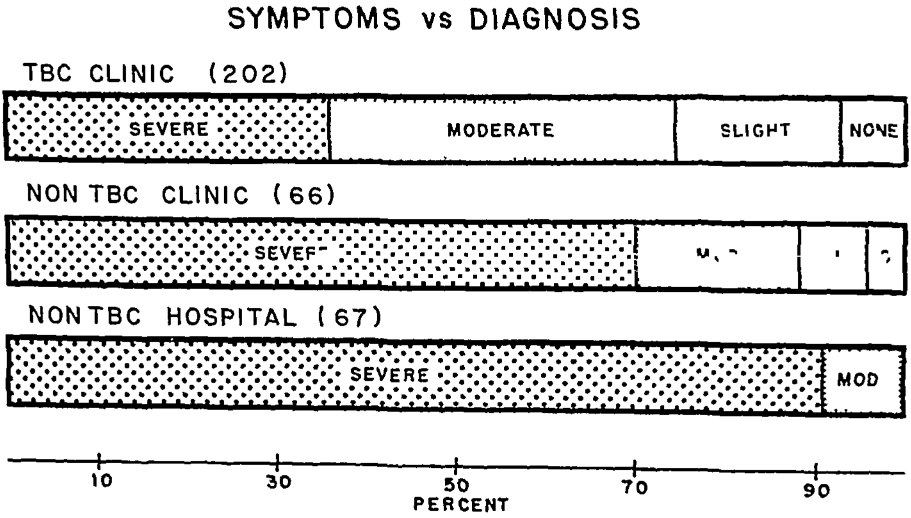

FIGURE 3

by non-relatives who consisted almost entirely of lodgers and of friends who came to visit or were visited frequently. The infections were all in home areas except one nine-year-old girl who contracted it from a 10-year-old classmate with advanced tuberculosis.

Symptoms of tuberculosis in children are variable and not specific, but they indicate that the child is not well and, therefore, are important. Of the above mentioned 335 Maybury-treated children 5.6 per cent were without symptoms both on history of present illness and on observation at the time of admission. The other 94.6 per cent had symptoms ranging all the way from a comatose state of meningitis to irritableness accredited prior to admission to such factors as teething and to lonesomeness for the mother who had gone to the sanatorium or had taken a job. The degree of symptoms experienced during the present illness had some correlation with where the diagnosis was made.

Of the 67 children having a diagnosis of tuberculosis made during a non-tuberculosis hospital admission, 91 per cent had severe and 9 per cent had moderate symptoms. When the diagnosis was made on 66 of the children in a non-tuberculosis clinic or doctor's office, 69.7 per cent had severe, 18.2 per cent moderate, 7.7 per cent slight, and 4.5 per cent had no symptom but were found on routine tuberculin testing. When the diagnosis was made on 202 children in the tuberculosis clinic, 36.1 per cent had severe, 37.6 per cent moderate, 18.4 per cent slight, and 7.9 per cent had no symptom. Most of the children who had been in the non-tuberculosis hospital and many of those in both clinic groups had had high fever and had initially received treatment for suspected pneumonia. Some of the tuberculosis clinic group had been treated in non-tuberculosis hospitals and clinics during the present illness before being checked as tuberculosis contacts. It is disturbing that a large number were treated in non-tuberculosis hospitals and non-tuberculosis clinics after having had a checkup as tuberculosis contacts, i.e., after having been identified as a potential case of tuberculosis. Of the 335 children there were 71 (21 per cent), admitted to the sanatorium who were being carried as "observation" cases subsequent to the contact checkup for tuberculosis. Of these children, 19 had negative tuberculin, being in the incubation period of tuberculous infection; seven had had negative tuberculin on the first checkup and positive later but were nevertheless continued on further observation; 38 had positive tuberculin at first contact checkup but it was apparently not considered to be significant and seven had an equivocal tuberculin reaction at the first checkup (in four cases the tuberculin test was not properly done, one did not return for a reading, one developed a generalized rash which confused the picture, and one had had BCG). Of these 71 children, the interval between their being placed on observation and their admission to the sanatorium was one to 12 months in 61 cases and one year or longer in 10 cases. In most of these cases between three and nine months delay in making the diagnosis had been permitted. The degree of symptoms during their present illness was severe in 35 children, moderate in 25, slight in eight, and there was no symptom in three children. Symptoms did not always coincide with extent of tuberculosis; for instance, two children with miliary disease had only slight symptoms.

Among these 71 children the most serious tuberculous lesions which had developed were 10 cases of miliary and/or meningitis and one case of advanced pulmonary tuberculosis. One of the meningitis cases had had a positive tuberculin reaction two years earlier. In an 11-year-old girl who had miliary tuberculosis and recent tuberculosis of the wrist, the tuberculin conversion had occurred in babyhood. In a 10-year-old girl with acute fulminating advanced pulmonary tuberculosis who required subsequent left upper lobe resection, the first contact checkup at two years of age had been negative but three months later the tuberculin was positive.

From the standpoint of drug efficacy, the most opportune time to treat tuberculosis is when the infection is fresh, active, and small.

Admittedly a large proportion of infected children will not develop clinical tuberculosis and for these the use of antituberculosis therapy following infection is unimportant but for those children who will develop progressive tuberculosis the use of INH and PAS at the time the infection is discovered is mandatory. In order to protect the few from progressive tuberculosis we must treat all the potential cases. Using drug therapy in the fresh small tuberculous lesion, even those not yet detectable, seems to us much more definitive than does withholding it for use in case the primary and/or extrapulmonary lesions progress and become more caseous and more walled off.

One never really feels safe in discontinuing therapy which is initiated for old—but still active—primary tuberculosis especially if associated with meningitis, tuberculoma of the brain or other extrapulmonary lesions. Compared with the fresh, small lesions, these old ones have a greater potentiality for causing drug resistance and for requiring future treatment.

It seems to us that it is not a problem as to whether or not to initiate specific therapy on the children with fresh, active tuberculosis but rather how to be able to start all such children without delay and to assure that the prolonged continuous course will be carried through to completion.

For the recent tuberculin converter with little or no x-ray film findings we would start isoniazid with 7 or 6 mg./Kg. per day divided into two doses and PAS 150-100 mg./Kg./day divided into three doses. The dosage would later be reduced to 5 mg./Kg. before the end of the year's treatment. Since we have been adding PAS to the isoniazid in cases having small visible lesions it seems indicated in invisible lesions also.

Isoniazid must be one of the drugs given to children. It is the most effective against meningitis. Five to 3 mg./Kg./day are effective in some cases but in those which happen to be rapid acetylators larger doses are indicated and B_6 could be given. Rarely does a child have intolerance to isoniazid. In the sanatorium our actual intolerance to PAS is low and its acceptance is a part of the sanatorium routine.

The recent tuberculin converter does not have stable lesions regardless of the degree of symptoms and signs. Therefore he should be started on INH-PAS and on a routine which will maintain him in an optimum state of health. He should have adequate diet with supplemental vitamins and special attention to nitrogen and calcium balance. He should be protected from colds, childhood diseases and intercurrent infections. Fatigue should be prevented. The amount of bed rest will depend on the symptoms and x-ray film findings. In the beginning some will need bed rest for the first few months. All should have at least a lying-down rest period in the morning, a sleeping rest period right after lunch and should go to sleep early at night. When any exercise is allowed a good portion of it should be designated for regular daily short periods of quiet play outside. If of that age, school should be allowed after a few months for the child who from the beginning was free of symptoms and x-ray film finding. A rest period should be taken when he returns from school.

A heavily exposed, tuberculin-positive baby should be given Isoniazid and PAS at once regardless of symptoms: We cannot justify waiting for an acute illness or confirmatory x-ray film findings before starting therapy. He more urgently needs treatment if he has x-ray findings which suggest "pneumonia" and particularly if he has acute symptoms of "pneumonia." We must not wait for culture reports but start antituberculosis and broad spectrum antibiotic therapy as soon as throat swabs, gastric washings and, if indicated, spinal fluid specimens are obtained. Should complete investigation rule out tuberculosis the antituberculosis drugs would be discontinued and no harm would have been done. However, if antituberculosis drugs are not used promptly and the child develops meningitis, miliary or some other form of serious progressive tuberculosis there would be no returning to the early advantageous starting point.

Experience with children who have run the gantlet from tuberculosis exposure through periods of neglect, "observation" misdiagnosis and delay tends to crystallize, several points in recommending the procedure in handling such cases.

Since the tuberculin test is the most specific of all procedures and can detect tuberculosis whether or not there are symptoms and other findings, it should carry the most weight in making an early diagnosis of tuberculosis in children. In order for a positive tuberculin test to represent active tuberculosis it must be supported in some of the following ways: (a) by a recently dated previous negative tuberculin reaction, (b) by the associated symptoms and/or x-ray evidence of active tuberculosis, (c) by the demonstration of tubercle bacilli in collected specimens, (d) by finding among the close associates an "open" case of tuberculosis of recent origin, or (e) by the young age of the child. Certainly if the child is under one year of age the disease could be considered as active and as probably active if the child is two or even three years of age but in a six-year-old child, age would definitely *not* be confirmatory evidence. If the father had

had a negative employment x-ray film nine months previously and now is an open case of tuberculosis there is certainly strong presumptive evidence that a positive tuberculin test in his son represents fresh, active tuberculosis regardless of symptoms, x-ray findings, or age.

As early as we can find active tuberculosis we must treat specifically to secure the earliest and best possible healing. During a delay of three or more months untreated primary lesions of any size may undergo considerable caseation in which tubercle bacilli can more effectively barricade themselves. Once the primary infection has been allowed to go untreated, future routine follow-up chest x-ray films are no insurance against tuberculous meningitis, reinfection tuberculosis or a lumbar spine lesion. (One wonders what proportion of the present day geriatric tuberculous patients had onset of tuberculosis in childhood.)

The oldtime standard of a three-month interval between tuberculosis checkups should be discarded during the early observation period of recently exposed children.

The child who has a negative tuberculin test when first checked as a tuberculosis contact is in a potentially dangerous, if not already in an actually dangerous situation. If he is sick he could be anergic from overwhelming tuberculous infection; if he is healthy he may be in the incubation period of his infection.

Above all we don't want to give the parents of these apparently healthy, heavy contact, negative tuberculin babies a false sense of security during such a potentially dangerous time as the first three months after he is removed from heavy exposure. Within these three months the baby may become tuberculin positive, develop a generalized spread and marked symptoms. If at the first contact checkup at the tuberculosis clinic there is proper orientation of the mother on the daily recording of the child's temperature and all his symptoms and bringing him every few weeks for scheduled clinic appointment for observation and repetition of the (negative) tuberculin test for at least two months, we should be able to practically prevent this type of baby being treated unsuccessfully for bronchopneumonia and then worked up from a tuberculosis standpoint elsewhere and finally referred back to the tuberculosis clinic or admitted to the sanatorium.

Admission to the sanatorium makes it easier to complete the investigation and to start the child on his drug and rest schedules. It gives the parents a better insight into the course of treatment in store for the child and also it gives the illness-wrecked home a chance to get organized for the job of cooperating with the clinic in caring for the child after he is discharged from the sanatorium. A child whose lesions are stabilizing under well-tolerated drug therapy is better off in a good reliable home where life is more normal and it is easier to prevent intercurrent infections and contagious diseases. However, it is lack of reliability on the home front which leads to abuse of drug therapy and is the problem most likely to be insurmountable in the early adequate treatment program.

There will always be some children who will need to take all of their treatment course in the sanatorium since releasing them to the home would be tantamount to discontinuing treatment.

With a program of early specific therapy fewer patient sanatorium days will be required, but in order to reach this goal there will be required (1) a lot of capable cooperation from the child's family, and (2) an increase in clinic and field personnel. There must be dependable people who will keep check on how the treatment program in the home is being carried out, on the failure to keep clinic appointments and many other factors associated with completing the treatment of a tuberculous child in the home. We probably should enlist, train, and supervise a militia of mothers and grandmothers rather than increase the standing army of nurses and medical attendants in the sanatorium. In this way the little patients will move through the limited number of sanatorium beds at a rate which will permit the necessary therapy being given to all these children at the most advantageous time.

The following cases will illustrate and somewhat summarize what has been said above.

Case 1: Denise, a Negro girl, lived in the same home with her aunt in April and May of 1952 but when this aunt was hospitalized for tuberculosis two months later, the child was not checked as a "contact" case but showed up as a pilot case a year later—almost a year too late. Her mother did not notice symptoms until about May 15, 1953 when she developed a cold which became more severe and was thought to be pneumonia. On June 17, 1953, she was seen in a non-tuberculosis clinic and on June 18, in a second clinic where patch test and x-ray film were found to be *positive and she* was admitted to Maybury Sanatorium on June 19, 1953 as a semi-emergency. She was four years old, acutely ill, listless, 25 per cent underweight and had a troublesome, brassy, productive cough. The sputum was positive for tuberculin bacilli on both smear and culture. Her x-ray film showed extensive lymph node enlargement

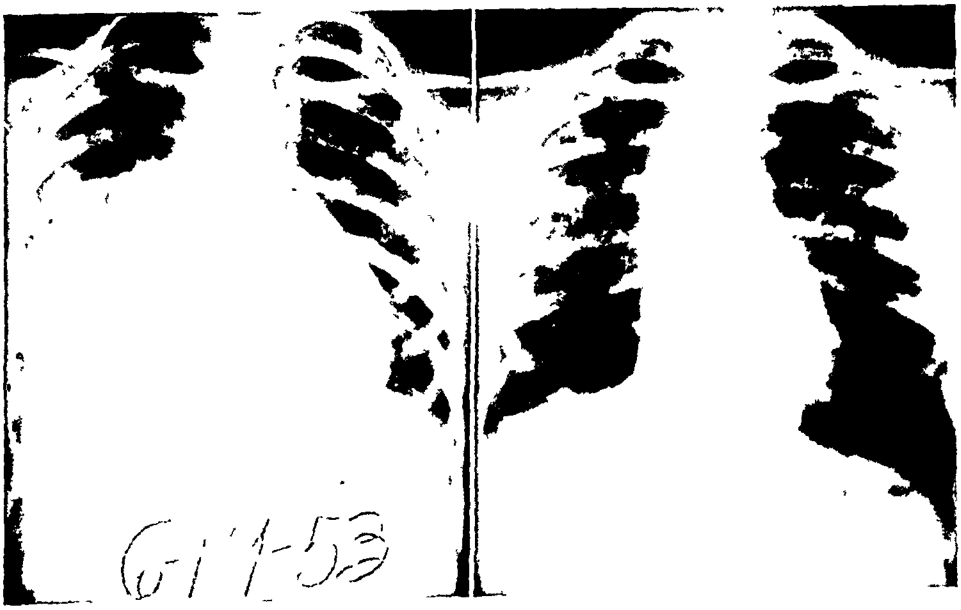

FIGURE 4A FIGURE 4B

Figure 4A (Case 1): Admission on June 19, 1953. Dense infiltrations in lower 2/3 right lung with 2 cm. cavity and extensive lymph node enlargement at and above the right hilum.—*Figure 4B:* Taken on June 21, 1955 showing the clearing after 2 years of antimicrobial therapy. There is atelectasis of right lower and middle lobes with extensive saccular bronchiectasis.

at and above the right root and a large complicated primary lesion with a 2 cm. cavity in the lower two thirds of the right lung. After two years of INH plus SM and/or PAS therapy there was marked clearing. At this time a bronchogram demonstrated marked contraction of the middle and lower lobes into a small space near the heart. There was extensive saccular bronchiectasis in both these collapsed lobes which were surgically removed. The surgical specimen showed not only the atelectasis, fibrosis, and bronchiectasis but also partially calcified caseous tissue containing tubercle bacilli. (These failed to grow out in nine months of culturing.) The operation was long and tedious due to fibrosis extending into and around the root of the lung. Calcifying mediastinal lymph nodes remained. Her postoperative course was uneventful and after a total of 32 months in the sanatorium she was allowed to go home to continue INH-PAS in the Chemotherapy Clinic for an additional year.

Case 2: Richard, a white boy, was 17 months old when his mother was hospitalized with advanced tuberculosis and a history of cough for six months. The mother absconded twice and at no time was Richard checked as a contact. He seemed to do well until about five years old when he began to chill and tire easily. Four months later (a month before admission to Maybury) he had occasionally frontal headaches and his right eye seemed to turn inward. A week or so later he awoke one morning with right-sided paresis and convulsive movements. He had difficulty walking, slurred speech, urinary incontinance, drooling, and intermittent fever. Three weeks later the jerking movements were more severe, he was choking on his saliva and was having trouble hearing. He was finally taken to a non-tuberculosis hospital where an intracranial tumor was diagnosed. A positive Mantoux test, and hilar calcifications were found. Spinal fluid was normal. SM-INH-PAS were started on the presumptive diagnosis of tuberculoma of the brain. Therapy has been continued since his admission to Maybury on July 28, 1955, and he has responded well except for some residual paralysis of face, left hand, and both feet. He is able to get about in a walker. Therapy is being continued.

Case 3: Larry, a Negro boy, had BCG at four days of age in September, 1955, the same month in which his father's pre-employment x-ray film showed pulmonary tuberculosis. The father was admitted to the sanatorium when Larry was six weeks old but absconded after one month and was not rehospitalized until Larry was seven months old.

At one month of age, Larry had first contact checkup in the tuberculosis clinic. Tuberculin test was negative. At two months of age he was seen in a non-tuberculosis clinic because of fever and irritability and was treated for pharyngitis. On the second non-tuberculosis clinic visit he had cough and frequent loose stools. On the third visit there, after a month of symptoms, tuberculin test was four plus and x-ray film

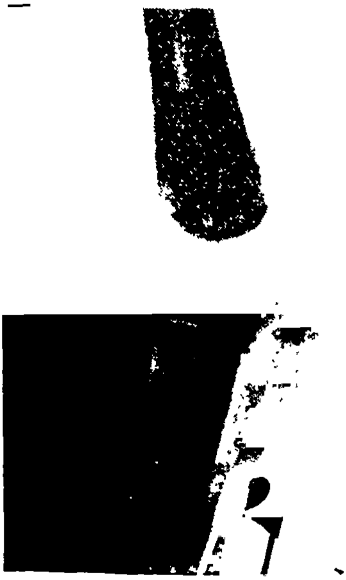

FIGURE 5 (Case 3): X-ray film of right elbow showing destructive process in ulna with posterior dislocation and gross soft tissue swelling.

strongly suggestive of tuberculosis. He was referred to the tuberculosis clinic where the diagnosis of active primary tuberculosis was made. In the next three weeks he was seen three times in the non-tuberculosis clinic with coughing, sweating, rhonchi, wheezes, and fever to 104.4°. He was again referred to the tuberculosis clinic but did not go there until more than two months later. Shortly afterward he again began to have a high fever, this time accompanied by a hot, painful, swollen elbow and after a week of these symptoms was seen in a different non-tuberculosis clinic. Tuberculin test was again positive. X-ray film showed hilar adenopathy and "probable tuberculosis of the elbow." The elbow was surgically drained and cultures were subsequently reported positive for tubercule bacilli. He was started on INH and SM and after two months he was transferred to Maybury Sanatorium on June 8, 1956, when nine months of age. He was overweight, afebrile, and had a swollen elbow with draining sinus.

On x-ray film the right elbow showed posterior dislocation of the ulna and considerable destruction of the articulating surface of the ulna and extensive soft tissue swelling. The chest x-ray film showed questionable lymph node enlargement and parenchymal lesion on the right side. Isoniazid-streptomycin were continued and PAS added. Four months later SM was discontinued. A month after admission the sinus had closed. At present he has a completely functional and normal appearing elbow.

Case 4: Paul, a two year old white boy, was admitted to Maybury April 22, 1957, with history of exposure dating back four to eight months. After his grandfather, in whose home he visited frequently, was hospitalized with advanced tuberculosis March 11, 1957, Paul had his first contact checkup. Mantoux was found to be positive. About February 13, 1957, he became irritable, had anorexia, marked weight loss, and sore throat. He was treated in two different doctors' offices and then admitted to a non-tuberculosis hospital because of continuing symptoms, fever of 104° F. and vomiting. In the hospital it was necessary to have tube feeding. His symptoms had been considered due to nervousness because his mother had gone back to work. His x-ray film showed a well developed, fine (fatal-type) of miliary tuberculosis. He was started on INH-SM-PAS and transferred to Maybury Sanatorium where on continued drug and supportive treatment he is showing good improvement.

Case 5: Kenneth's first contact checkup was 12 days before his mother's rehospitalization. He was still in the incubation period and, therefore, tuberculin test and x-ray film were negative. This gave a false sense of security and he was scheduled for routine checkup in three months. Two weeks after this x-ray film inspection and a few days after his mother was hospitalized he began to lose weight, have frequent colds, and be irritable. This was thought to be due to lonesomeness for his mother. After two weeks of symptoms he was seen in a non-tuberculosis clinic for the first time and only this extreme irritableness was found then and at the second clinic visit three days later. On the third and fourth non-tuberculosis clinic visits, temperature was 101° F. and he was treated for ear and throat infections. Six weeks later he was listless, feverish, coughing and vomiting and having difficulty walking. After 10 days of treatment in the doctor's office he was referred back to the non-tuberculosis clinic for hospitalization but when x-ray film showed evidence of advanced miliary tuberculosis

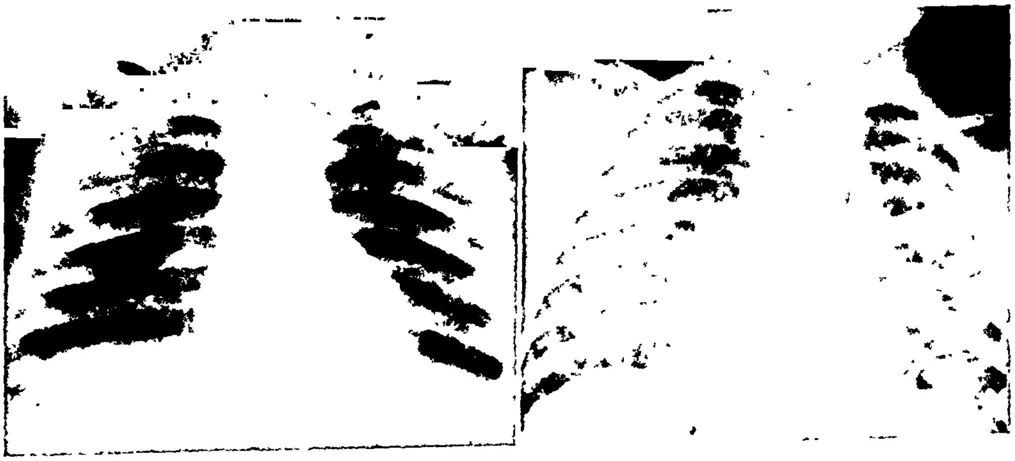

FIGURE 6A FIGURE 6B

Figure 6A (Case 5): Opened on January 10, 1955. Contact checkup film was normal.—*Figure 6B:* Admission film taken July 19, 1955 shows extensive miliary tuberculosis, he was admitted to Maybury as an emergency. The tuberculin test was positive and cultures of swallowed sputum were positive for tubercle bacilli. Spinal fluid was normal.

He had fever, shortness of breath, dusky pallor, constant distressing cough, and marked fatigue. He was placed in the oxygen tent and given isoniazid and streptomycin in high dosage and PAS in routine dosage and is making a good recovery.

SUMMARY

Every effort must be made to advance the diagnosis and management of early tuberculosis in children. The proper use of the tuberculin test will help do this. A positive tuberculin test is specific and is diagnostic of active tuberculosis in a child if he is very young, if it is preceded by a recent negative test, if it is associated with known contact with an "open" case of tuberculosis or if it is suported by clinical, x-ray film or laboratory findings.

The value of x-ray film in diagnosing early tuberculosis in children is definitely limited because it is difficult to obtain a good roentgenogram, the lesions may be obscured by intrathoracic structures, the shadows may be mistaken for other types of disease and because there is nothing specific about early primary tuberculosis lesions, the lesions may not have developed to the extent that they can be demonstrated by x-ray film.

Case history is extremely important including dates—dates of contact, of onset of symptoms, of negative and positive tuberculin tests and of negative and positive x-ray film findings. Among 335 children treated in Maybury Sanatorium since January 1, 1956, the age of onset was under five years in more than 75 per cent. These home infected children should serve as "pilots" in searching for "open" cases of tuberculosis. The source of contact was found among members of the family in 35 per cent and among other close relatives in 34 per cent of the cases. In 15 per cent the contact was an uncooperative tuberculous patient.

Symptoms are variable but not specific. Nearly 95 per cent of the 335 children had symptoms. Cases diagnosed in non-tuberculosis hospitals and clinics were more likely to have severe symptoms than those diagnosed in the tuberculosis clinic. Many children known to be exposed and/or infected were treated for various other conditions before the real cause of illness was suspected. During these periods of time some of these children progressed to serious tuberculosis—five such cases are presented. A plea is given to discard the routine three-month interval between checkup examinations in the management of early tuberculosis in children. Serious progression often occurs within three months.

Antimicrobial therapy must be used at the earliest possible time in tuberculosis in children—i. e., when the tuberculin converts or if the child has had heavy exposure and is sick (anergic). The younger or the sicker the child the more urgent is treatment. We use Isoniazid 7-6 mg./Kg./day with PAS 150-100 mg./Kg./day. It is tolerated well and no harm will result from its use in suspected cases but if not used and the child develops serious tuberculosis there is no way to recover the early advantageous point which was missed.

We urge that more attention be given to tuberculosis in young children. We advocate the tuberculin testing of all pre-school children in clinics and

doctors' offices and the proper handling of all positive reactors. We recommend early treatment of all cases, in the hospital preferably for the initial part and in the properly organized home for the completion.

RESUMEN

Debe hacerse toda clase de esfuerzos para adelantar el diagnóstico y el tratamiento de la tuberculosis primaria en los niños. El adecuado uso de la tuberculina ayudará para esto. Una reacción positiva de tuberculina es específica y diagnóstica de tuberculosis activa en un niño si es muy joven, si además es precedida de una reacción negativa reciente, si se sabe que está en contacto con un caso "abierto" de tuberculosis o bien si esto se apoya en la investigación clínica, radiológica o de laboratorio.

El valor de los rayos X para diagnosticar la tuberculosis primaria en los niños, es francamente limitado por la dificultad de obtener buenas radiografías; las lesiones por otra parte pueden ser ocultadas por las estructuras intratorácicas; las sombras pueden ser tomadas equivocadamente por otra enfermedad y como no hay nada específico referente a las lesiones de tuberculosis primaria, éstas pueden no haberse desarrollado hasta el grado de poderse demostrar en la película de rayos X.

La historia clínica es muy importante incluyendo fechas de contacto, de principio de síntomas, de pruebas negativas y positivas de tuberculina, y de los hallazgos positivos a los rayos X.

Entre 335 niños tratados en el Sanatorio Maybury desde Enero de 1956, la edad del principio fué bajo los cinco años en más de 75 por ciento de los casos. Estos niños infectados en sus casas deben servir como "pilotos" para buscar los casos abiertos. La fuente de contacto fué encontrada entre lo miembros de la familia en 35 por ciento de los casos y entre otros parientes próximos en 34 por ciento. En 15 por ciento el contacto era un enfermo no deseoso de cooperar para la protección.

Los síntomas son variables pero no específicos. Aproximadamente 95 por ciento de 335 niños tenían síntomas. Los casos diagnosticados en hospitales que no son para tuberculosos y en las clínicas posiblemente presentan más frecuentemente síntomas más severos que los diagnosticados en las clínicas de tuberculosos. Muchos niños conocidos como expuestos y/o infectados se trataron por otras causas antes de que la causa real de su enfermedad se sospechase. Durante estos períodos de tiempo algunos de los niños marcharon hacia tuberculosis grave. Cinco de tales casos se presentan. Se reclama que se descarte el intervalo de rutina, de tres meses entre los exámenes en el control de la tuberculosis primaria. Serios avances de la enfermedad a veces ocurren durante tres meses.

La terapéutica antimicrobiana debe usarse tan tempranamente como sea posible en la tuberculosis infantil ya sea cuando la tuberculina vira o aún antes si el niño está altamente expuesto.

Mientras más joven o más enfermo parezca el niño, más importante es el tratamiento. Nosotros usamos isoniacida 7-6 miligramos por kilo por día asociando PAS 150-100 mgrms. por kilo pordía.

Esto es bien tolerado y ningún daño resulta de su uso, pero si se nota que el niño presenta tuberculosis grave no hay manera de recuperar las ventajas que al principio se han perdido.

Urgimos que se ponga más atención en la tuberculosis entre los niños muy pequeños. Aconsejamos la prueba tuberculínica en todos los niños pre-escolares en las clínicas y en los consultorios de los médicos, así como aconsejamos el trato adecuado de todos los reactores positivos. Recomendamos tratamiento temprano en todos los casos en el hospital de preferencia para la iniciación y el hogar bien organizado para la continuación.

ZUSAMMENFASSUNG

Es muss alle Anstrengung unternommen werden, um die Diagnose und die Behandlung der kindlichen Frühtuberkulose zu fördern. Die entsprechende Anwendung des Tuberkulintestes wird dazu beitragen. Ein positiver Tuberkulintest ist spezifisch und ist gleichbedeutend mit der Diagnose einer aktiven Tuberkulose bei einem Kind, wenn es sehr jung ist, wenn in diesem Fall kürzlich erst eine negative Probe vorausgegangen ist, wenn er gleichzeitig auftritt mit einem bekannten Kontakt mit einem "offenen" Fall von Tuberkulose, oder wenn er unterstützt wird durch Klinische, röntgenologische oder Laboratoriums befunde.

Der Wert von Röntgenaufnahmen bei der Diagnose einer frühen Kindertuberkulose ist fest begrenzt, da es schwierig ist, eine gute Röntgenaufnahme zu erhalten, ferner die Herde verdeckt sein können durch intrathorakale Körperteile, weiter die Schatten irrtümlich für eine andere Krankheitsart gehalten werden können und schliesslich—weil nichts besonders kennzeichnend ist für frühe tuberkulöse Primärherde—die Herde sich vielleicht noch nicht so weit entwickelt haben, dass sie sich durch eine Röntgenaufnahme nachweisne lassen.

Die Vorgeschichte ist von ausserordentlicher Wichtigkeit, inbegriffen die Zeitangaben—Zeitangaben über Kontakt, Beginn der Symptome, des negativen und des positiven Tuberkulintestes und von negativen und positiven Römtenaufnahmenbefunden. Unter 335 im Maybury-Sanatorium seit 1.1.1956 behandelten Kindern betrug das Alter zu Beginn der Erkrankung in mehr als 75% weniger als 5 Jahre. Diese in ihrer Häuslichkeit infizierten Kinder müssen als "Lotsen" dienen auf der Suche nach "offenen" Fällen von Tuberkulose. Die Infektionsquelle fand sich unter Familienangehörigen in 35% und unter anderen näher Verwandten in 34% der Fälle. In 15% war die Quelle ein asozialer tuberkulöser Patient.

Die Symptome sind variabel, aber nicht spezifisch. Etwa 95% der 335 Kinder hatten Symptome. Bei Fällen, die in nicht tuberkulösen Hospitälern und Ambulanzen festgestellt waren, war es wahrscheinlicher, dass schwere Symptome bestanden, als bei solchen, die in Tuberkulose-Anstalten diagnostiziert wurden. Viele Kinder, von denen bekannt wra, dass sie exponiert waren und die oder die infiziert worden waren, wurden auf verschiedenste andere Krankheiten behandelt, ehe man die wahre Krankheitsursache vermutete. Während dieser Zeitabschnitte entwickelte sich bei einigen dieser Kinder Eine Schwere Tuberkulose. Über 5 solcher Fälle wird berichtet. Es wird dafür eingetreten, sich frei zumachen von den routine-mässigen 3-monatigen Intervallen zwischen der genauen ärztlichen Durchuntersuchung bei der Betreuung der frühen Tuberkulose bei Kindern. Es kommt oft zu bedenkliche Progredienz innerhalb von 3 Monaten.

Antimikrobielle Therapie muss angewandt werden zum frühest möglichen Zeitpunkt bei der Kindertuberkulose-, d-h- wenn die Tuberkulinprobe von Negativ zu Positiv umschlägt oder sogar noch vor diesem Zeitpunkt, sofern das Kind stark exponiert gewesen war. Je jünger oder je mehr schwer krank das Kind ist, desto wichtiger ist die Behandlung. Wir gebrauchen INH 7-6mmg-kg-tägl. mit PAS 150-100mmg-kg-tägl. Dies wird gut vertragen und dieser Modus hat keinen Schaden zur Folge bei verdächtigen Fällen; wird davon aber kein Gebrauch gemacht, und bei dem Kind entwickelt sich eine schwere Tuberkulose, gibt es keine Möglichkeit, die frühen vorteilhaften Stufen wieder-zugewinnen, die verpasst wurden.

Wir betonen nachdrücklich dass der Tuberkulose bei Kleinkindern mehr Aufmerksamkeit gewidmet werden muss. Wir befürworten die Tuberkulinprüfung aller Kinder im Vorschulalter in Ambulanzen und ärztlichen Sprech-Stunden und die geeignete Handhabung aller Fälle mit positiver Reaktion. Wir empfehlen die Frühbehandlung aller Fälle und zwar stationär vorzugsweise für die Einleitung der Behandlung und in entsprechend organisierter Häuslichkeit für den Abschluss.

BIBLIOGRAPHY

Myers, J. A.: "Tuberculosis Among Children and Adults," Third Edition, Charles C Thomas, Publisher, Springfield, 1951.

The Struggle for Eradication of Tuberculosis

IRVING WILLNER, M.D., F.C.C.P.*
Newark, New Jersey

Advances in drug therapy have required changes in public health procedures without discarding the time tested practices of tuberculosis control. Chemotherapy and modern advances in thoracic surgery have resulted in a sharp drop in mortality, declining morbidity, shorter duration of treatment and diminished hospital confinement. No known single or combination of drugs destroys all tubercle bacilli in the body and the outlook for improved therapy must depend upon research laboratories. Our present anti-tuberculosis drug therapy fails in some cases and has no effect on those infected with drug resistant bacilli. Among others with widespread bilateral disease, especially the elderly, active disease cannot be arrested and such persons must be isolated.

Prior to the advent of streptomycin, therapy depended largely on bed rest, nutrition and collapse procedures. Treatment was largely in the hands of specialists in pulmonary disease and only a small percentage of patients was under the care of general practitioners. The average physician could not spare the time necessary on a single patient for proper coverage of medical advice and treatment after making a diagnosis of active disease. The case was referred to a sanatorium or to the phthisiologist. Modern drugs have simplified therapy, and physicians who never treated tuberculosis under the old regime, are now taking care of many ambulatory patients. The doctor now specializing only in tuberculosis is a rarity. A result has been that more patients are refusing hospitalization because they or their physician rejects institutional care. Our problem, now is not only with the "good chronic," with lingering tuberculosis and positive sputum, who is allowed to go about his occupation, meantime spreading the disease, but also with early, and moderately advanced cases under therapy who form an added source of infection. Patients without hospital supervision have been arrested, but more have progressed to advanced stages before being sent to institutions. Widespread practice of ambulatory chemotherapy has resulted in development of drug resistant organisms in a number of cases. The unhospitalized tuberculosis patient is a major health problem, as a source of infection.

Mortality

Records for the past half century show the steady drop in mortality rate. In spite of the declining rate, tuberculosis is still responsible for more deaths than all other infectious diseases combined. Once a disease of young adults, the problem now concerns the aged, especially old men. Prior to the advent of anti-tuberculosis drugs, bed rest and collapse therapy helped the rate to fall. Subsequent to that time, campaigns to locate the disease before it was too widespread, and improved medical and surgical treatment resulted in a sharp decline of fatality rate. The first eight years following the use of streptomycin and later other anti-tuberculosis drugs, demonstrated our most rapid decrease of mortality in history. The sharp drop slowed in 1954 when a plateau was reached in curbing tuberculosis deaths. In 1955 the same death rate occurred as the previous year, and in 1956 there was a rise. The drugs have not been controlling the disease in all cases and in some instances, the bacilli have been reactivated. Some individuals kept alive by modern therapy and apparently arrested, have reactivated and died.

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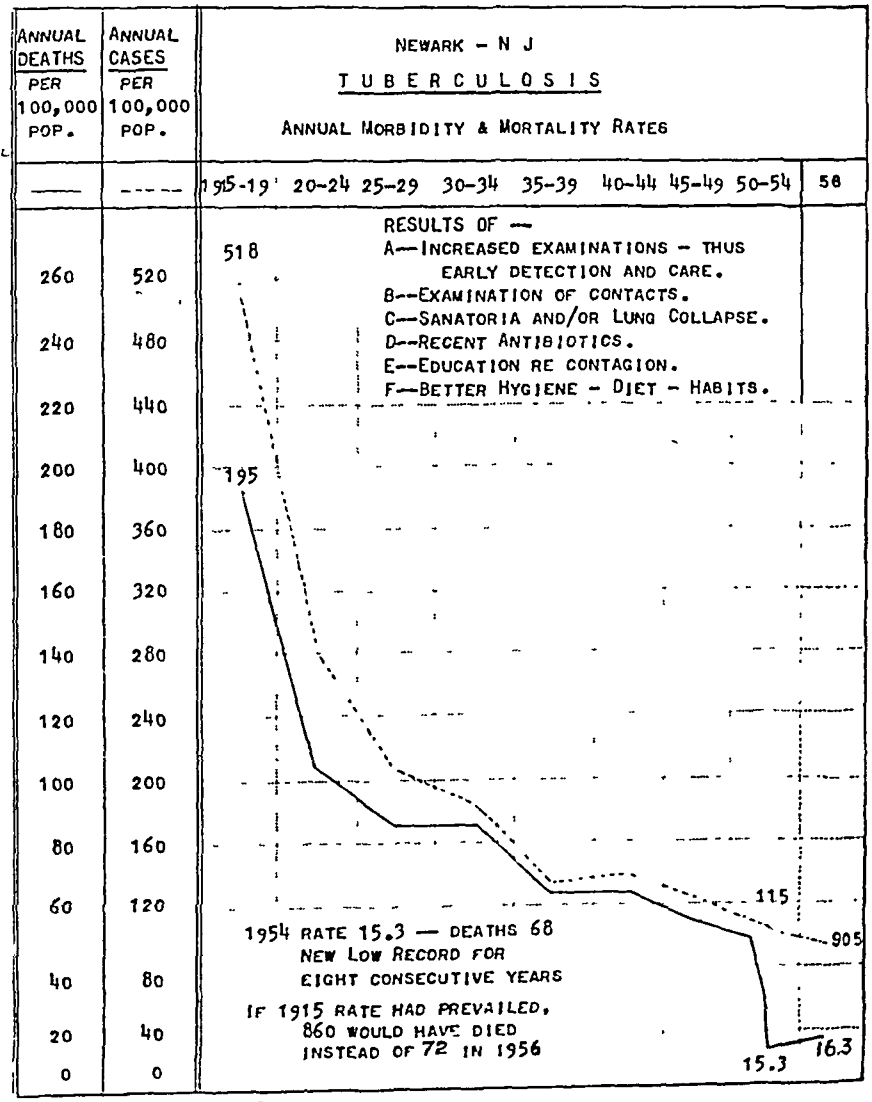
*Director, Chest Disease Bureau, Newark Department of Health and Welfare.

Morbidity

The morbidity rate has been declining for several years but not as rapidly as the death rate. The drop in the annual incidence of tuberculosis would suggest that the number of cases infected is declining. This may lead to an impression with the falling death rate that tuberculosis is becoming a minor problem. In dealing with a disease characterized by



chronicity and relapses, an arrested case can flare into activity. Some individuals probably harbor the tubercle bacilli since childhood, while others contract it in adult life. The apparently arrested and inactive case can still harbor live tubercle bacilli which can be reactivated. The arrested case with stationary x-ray findings may still have small necrotic lesions that can flare into progressive tuberculosis. The most lucrative source of case finding is still the family contacts of an active or suspicious case. Epidemiological investigation of family contacts results in discovery of more new infections that perpetuate tuberculosis than any other method. The decreasing morbidity rate does not confirm estimates of the Public Health Service of 400,000 active cases of tuberculosis in the United States and twice that number of inactive cases.

Newark, New Jersey, is an industrial city with a population estimated at 443,000 (360,000 whites, 83,000 negroes). Tuberculosis control program is based on:

1. Mass x-ray film surveys throughout the city with spot checkups in areas where the tuberculosis incidence is high.
2. Tuberculin testing of children with x-ray film and follow-up, not only of the positive reactors but of members of the families and other contacts.
3. Isolation of the open active cases.
4. Improved medical and surgical procedures of therapy.
5. Close supervision of all contacts.
6. Commitment of cases that refuse to co-operate and form a public health menace.

The unknown case is responsible for a substantial amount of infection. This source is far more dangerous than our known cases. Some patients have been diagnosed but never reported to the public health authorities. A few undiagnosed and untreated cases can start a new epidemic of tuberculosis. Regardless of all case finding methods, many are never located. They have neither been recognized nor diagnosed until just before or after death. Since the advent of chemotherapy, this great hazard has been increasing. The following chart illustrates the percentage of unknown cases in Newark, N. J., reported after death.

	Per Cent		Per Cent
1944	24	1951	21
1945	20	1952	22
1946	24	1953	29
1947	22	1954	22
1948	21	1955	30
1949	23	1956	39
1950	37		

X-ray Film Surveys

When subjective complaints are absent and there is no clinical finding, the x-ray film is the most powerful instrument in locating minimal lesions. An early diagnosis helps not only in locating the source of infection but gives an excellent chance for complete recovery. X-ray film surveys have been conducted annually for a number of years on a voluntary basis. The essence of the survey is to locate the active or suspicious case. Most individuals will have had no contact with an infectious case, but cases without known contact can be located. Success of the survey with mobile and stationary units largely depends upon the *preliminary educational program.* Preceding a campaign, in an effort to reach a large segment of the population, the local press, radio, addresses before social and fraternal groups, motion pictures, placards in buses, and a sound truck are utilized. The drives are intensified in "high incidence or target areas" where statistics demonstrate most active cases reside. A major problem is to attract to the units, individuals most likely to harbor tubercle bacilli. The derelict, the chronic alcoholic and floater found in slum areas and in poor housing districts usually avoid survey. Some individuals knowing or suspecting that they have tuberculosis do not respond as they do not want to be known to health authorities. The screening forms only an initial step. Without an intensive follow-up, the entire program is a waste of public funds.

The value of a survey can be estimated in: 1. Stimulating public interest in tuberculosis. 2. Locating cases that have been arrested for many years that have reactivated. 3. Finding inactive cases and following up new contacts. 4. Discovering other pulmonary abnormalities (pneumonia, pneumoconiosis, fungus infections, malignancy etc.) 5. Noting cardiac enlargements and reporting these to the family physicians.

Surveys include only a small percentage of the population, leaving the majority without examination for spreaders of the disease. A negative chest film is no assurance that active, progressive disease may not take place in the future.

Present case finding methods are far from satisfactory and repeated surveys have resulted in locating only a small percentage of active cases that were not previously known.

Tuberculin Test

The tuberculin test, an economic method of case finding, is the best diagnostic tool for determining the absence or presence of infection. A positive reaction indicates that tubercle bacilli have been present and may still be viable. The positive reaction in infants is usually the only evidence of tuberculosis infection, and suggests a close contact with an

ACTIVE CASES OF PULMONARY TUBERCULOSIS LOCATED *IN MASS X-RAY SURVEYS*

Year	X-Ray Films Taken	Active Cases (Not known to Health Dept.)
1953	39,002	17
1954	8,811	8
1955	7,295	7
1956	32,728	11 (80 per cent complete)

active case. Among those who react to tuberculin only a small percentage develop active disease and a long time may elapse between the reaction and the inception of clinical disease. Tuberculin surveys are essential in any public health program. Reactors are potentially active cases and must be followed with x-ray films well into adult life. Tuberculin testing in clinics and in public and parochial schools has been a regular procedure for many years. Not only are the reactors closely followed but also all members of the family and contacts. As the rate of infection decreases, the test is assuming a more prominent place in case finding. The test is important in finding unknown cases of tuberculosis, in diagnosis, and at times, furnishes information as to when infection took place. In routinely testing children, especially when there has been contact with an active case, the time of infection can be estimated when a persistently negative reactor changes to positive. In testing various groups of the population, an index can also be obtained as to which group requires more attention from an epidemiological standpoint. Every reactor should be treated as many will not require medical aid. However, recent convertors should be placed under chemotherapy.

There has been a remarkable decline in the number of reactors during the past 20 years. In the clinic of the Newark Division of Health (where a large portion have been exposed to tuberculosis at home, or where a relative or friend is ill with tuberculosis or where a member of the family died of the disease) the rate is higher among the school children.

In 1935 a survey of 997 children tested produced the following results:

	Number	Negative	Positive
White Children	657	478 — 61 per cent	281 — 39 per cent
Negro Children	229	132 — 44 per cent	167 — 56 per cent

The drop in reactors after 20 years is indicative of the lower proportion of infected children.

1955	1400		163 — 11.6 per cent
1956	1574		186 — 11.8 per cent

Most children tested at the Division of Health are also tuberculin tested at their schools. The majority of the pupils, however, are not known contacts. The following results were obtained:

PAROCHIAL SCHOOLS

(Children tested in all grades)

Year	Number	Positive	Per Cent
1955	3476	224	6.1
1956	4722	220	4.7

PUBLIC SCHOOLS

Tuberculin testing is routine in Grades 9, 10 and 12, except where known contacts are tested in any grade.

Year	Number	Positive	Per Cent
1955	10,372	534	5.2
1956	14,613	1079	3

Follow-up of reactors by x-ray films in active cases of tuberculosis (that were rested. Of the active cases: four were in the Kindergarten to sixth grade, one was in the seventh grade, two in the ninth grade and five in the tenth to twelfth grades.

Incidence of tuberculosis in children can be considered as a yardstick of prevalance of tuberculosis in a community. Evaluation of mortality statistics demonstrates the decline in children under 15 years of age when compared over a period of 20 years.

TUBERCULOSIS DEATHS AMONG NEWARK CHILDREN

	White	Negro		White	Negro
1931	7	21	1951	2	3
1932	9	13	1952	2	4
1933	17	16	1953	2	6
1934	7	10	1954	....	2
1935	8	14	1955	....	2
1936	1	16	1956	1	3

Eradication

Tuberculosis is far from being controlled in spite of education, research and modern medical and surgical therapy. Mass x-ray film surveys will not lead to eradication but may help to diminish the incidence. The tuberculin test should be widely used not only in children but in controlled groups of adults. (School teachers, municipal employees, domestics, food handlers) to locate positive reactors, who must be closely supervised. Every open active case must be isolated and treated and all contacts closely followed up by routine x-ray films. Proper isolation of the known patient will prevent the infection from spreading and thus limit the "pool of communicable disease." The major problem consists of the surviving tuberculous individual with unhealed disease who flares into activity. Eradication must depend upon the absence of infection and early diagnosis with rapid treatment to prevent further spread.

SUMMARY

1. Modern chemotherapy has simplified treatment in pulmonary tuberculosis and many active cases are now in the hands of general practitioners.

2. Mortality rates which have been steadily falling, appear to have reached a plateau.

3. Morbidity rates continue to drop leaving the false impression that tuberculosis is diminishing.

4. The unknown and undetected case forms the greatest hazard in a control program.

5. Mass x-ray film surveys only reach a small portion of the population and help to locate a small percentage of active cases.

6. Tuberculin testing and follow-up of the reactors forms the most lucrative method of case finding in a public health program.

7. The number of reactors in children is rapidly declining.

8. Eradication of tuberculosis can only be obtained by reducing the incidence of infection.

RESUMEN

1. La quimioterapia moderna ha simplificado el tratamiento de la tuberculosis pulmonar y muchos casos activos astán ahora en las manos de los médicos generales.

2. Las cifras de mortalidad que habían estado cayendo constantemente parece que han llegado a una meseta.

3. Las proporciones de la morbilidad continuan cayendo dejando la impressiòn falsa de que tuberculosis està disminuyendo.

4. Los casos desconocidos y no descubiertos forman el mayorpeligro en el problema del control.

5. La invesigaciòn por la roentgenfotografìa de las masas alcanzo sòlo una pequeña parte de la población y ayuda a localizar un pequeño porcentaje de casos activos.

6. La reacciòn tuberculìnica y el seguimiento de los reactores forma el método más fructífero de hallazgos en los planes de salubridad pública.

7. El número de reactores entre los niños está declinado rápidamente.

8. La erradicación de la tuberculosis puede sólo obtenerse reduciendo la incidencia de la infección.

ZUSAMMENFASSUNG

1. Die moderne Chemo-Theraphie hat die Behandlung der Lungentuberkulose vereinfacht und viele Fälle mit aktiven Befunden finden sich jetzt in den Händen von Allgemeinpraktikern.

2. Die ständig abfallenden Sterblichkeitskurven scheinen jetzt ein horizontales Niveau erreicht zu haben.

3. Die noch fortgesetzt abfallenden Morbititätskurven hinterlassen den falschen Eindruck, dass die Tuberkulose zurückgehe.

4. Die unbekannten und die nicht gefundenen Fälle stellen das grösste Problem dar bei der Tuberkulosebekämpfung.

5. Massenschirmbilduntersuchungen erreichen nur einen kleinen Teil der Bevölkerung und tragen dazu bei, einen kleinen Prozentsatz aktiver Fälle zu bestimmen.

6. Tuberkulin-Prüfungen und Nachkontrolle der positiv reagierenden Fälle stellen die am meisten lukrative Methode dar zur Fallsuche in einem Plan der öffentlichen Gesundheitspflege.

7. Die Zahl der positiv reagierenden Kinder geht rapid zurück.

8. Die Ausmerzung Tuberkulose lässt sich nur ermöglichen durch Verringerung der Infektionshäufigkeit.

Treatment of Pulmonary Tuberculosis with ACTH and Cortisone in Addition to Specific Anti-Tuberculosis Therapy

M. JESIOTR, M.D.*
Beer-Yacov, Israel

In these past years problems of the utmost practical importance have arisen in connection with the use of cortisone and ACTH for patients with pulmonary tuberculosis. Among them the following are outstanding:

1. Does the use of ACTH or cortisone have a deteriorating influence on an active tuberculous process and can it cause a relapse in non-active tuberculous changes?
2. Will a combined treatment, adding antimicrobial drugs to these hormones, prevent unfavorable phenomena as above described?
3. Will the combination of antimicrobial drugs with ACTH/cortisone influence the tuberculous process favorably?
4. And if so, are there indications for the use of steroids in tuberculosis? Which are the suitable doses and what is the average length of time for their use?

The first experiences with ACTH and cortisone in different diseases and especially in rheumatic diseases proved that not only in active but even in arrested tuberculosis the use of these drugs is contraindicated. Many cases have been observed in whom no tuberculosis was found prior to the use of these drugs and in whom severe active tuberculosis appeared after their use. In others a deterioration of inactive processes occurred or new disseminations were found.

Supported by these experiences, the American Trudeau Society warned in 1952 against the use of ACTH and cortisone in tuberculous patients. In their opinion, even a non-active tuberculous process is a danger, potentially, for the patient who is treated with these drugs to combat other diseases. In the past two years these views have undergone considerable change. A number of investigators have shown that ACTH or cortisone in combination with antimicrobial drugs not only are devoid of a negative influence on tuberculosis, but, on the contrary, can help in its cure.

These recent publications have served us as a stimulant to investigate this problem on a number of patients in our hospital. Investigations have been done on 29 patients with pulmonary tuberculosis of whom 14 had active, fresh processes, nine chronic pulmonary tuberculosis with exacerbations and six were chronics without exacerbations; besides one had residual intrapleural effusion following discontinuation of pneumothorax and one residual effusion after extrapleural pneumothorax, two exudative pleurisy with chronic pulmonary tuberculosis, and one chylous peritonitis of tuber-

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culous origin. There were also three with allergic rashes, two of which in the form of nonthrombocytopenic purpura as a complication after treatment with PAS and three with severe vertigo as a complication after treatment with streptomycin. In addition two had inactive pulmonary tuberculosis combined with severe asthma and two had cystic lung disease with asthma.

Methods

Treatment with ACTH and cortisone was given to patients ranging in age from three to 68 years. Excluded from the treatment were those suffering from hypertension, anamnesis of gastric or duodenal ulcer and diabetes mellitus. Before treatment was started, electrocardiogram, liver function test, blood electrolytes, Thorn test, and 17-ketosteroids in the urine, in addition to the routine examinations, were done. During the period of treatment with steroids the following examinations were made: Eosinophil count once weekly, 17-ketosteroids once in two weeks, electrolytes once in two weeks, electrocardiogram once monthly, x-ray film and tomogram at least once monthly, and screening twice weekly. Weight was controlled once weekly and in addition to all this, blood pressure was taken daily as well as examination of urine for sugar done every day and blood sugar once in two weeks. Children and adults, not older than 40, whose adrenals were regarded as in relatively normal condition, usually received ACTH. Adults over 40 and aged patients received cortisone or meticorten. The majority of cases with severe chronic tuberculosis received either cortisone or meticorten, assuming that the function of their adrenals might be impaired by their long-standing disease. Of course there is no absolute proof for this assumption. The determining factors were the auxiliary examinations. In those cases where the number of eosinophils rose above the level maintained prior to treatment and the amount of 17-ketosteroids in the urine sank, we changed the ACTH for cortisone or meticorten. Two weeks after termination of treatment we examined the function of the adrenals by means of the Thorn test and of eliminations of 17-ketosteroids in the urine. In the great majority of cases these examinations gave normal results. In single cases, where cortisone had been given for a longer period of time after which the above mentioned examinations gave unsatisfactory results, an additional treatment, consisting of 10 mg. ACTH daily for a period of seven to 10 days resulted in bringing back to normal the adrenalin function within one to two months. All except those who received meticorten were on a low-salt diet, with the addition of potassium either in the form of potassium chloride 1-2 Grams daily or in the form of orange juice which contains a sufficient amount of potassium.

The schedule of hormone administration was as follows:

Meticorten	Cortisone	ACTH Gel.
20 mg. daily for 10 days	100 mg. daily for 7 days	60 mg. daily for 5 days
15 mg. daily for 15 days	75 mg. daily for 7 days	50 mg. daily for 7 days
10 mg. daily for 20 days	50 mg. daily for 40 days	25 mg. daily for 30 days
5 mg. daily for 10 days	25 mg. daily for 5 days	12½ mg. for rest of treatment
2½ mg. daily for 5 days	12½ mg. daily for 3-4 days	

Administration of the hormones was gradually discontinued until the smallest doses were given towards the end of the course. Almost half of the patients received during the first period of investigation the hormones in the course of three months. The other half in the course of two months, in smaller doses. All the patients received antimicrobial treatment at the same time (streptomycin, PAS, INH simultaneously). The first cases were given streptomycin every day and the rest twice weekly. The results were similar.

Results

Analyzing results, we wish to emphasize on the clinical and radiological changes and the complications that occurred during the hormone therapy (Table I).

1. *Clinical Changes:* Temperature in all cases sank to normal during the first days of treatment and remained so for the rest of treatment as well as after its termination. The general condition of the patients underwent such a speedy and dramatic improvement as has, it is our impression, never been seen during antimicrobial treatment alone. It is worth noting already at this point, that not always has the above mentioned improvement been in accordance with the radiological one. In conjunction with the disappearance of toxic symptoms, an euphoria became apparent and the increase of appetite was such as to lead to immediate gain in weight, an average of more than 5 kilograms during the first month, and that not on account of a hidden edema (fluid imbalance), as weight remained unaltered also after termination of hormone treatment (Table II).

Cough and expectoration diminished rapidly, especially in fresh cases. Two cases of non-active tuberculosis and two with chronic cystic lung diseases, complicated by severe asthma, almost in status asthmaticus showed considerable improvement after two days and the improvement continued for the duration of treatment even with small maintenance doses. Two cases with non-thrombocytopenic purpura, three with an expanded allergic rash, and one of severe Quincke oedema as a result of streptomycin or PAS therapy, were cured in several days and the administration of the

TABLE I
RESULTS OF TREATMENT

	No. of cases	Good	Fair	No change	Deteriorated
Fresh tb:					
Mod. adv.	6	3	3	—	—
Far adv.	8	5	3	—	—
Total	14	8	6	—	—
Chronic tb:					
Without exacerbation	6	—	2	4	—
With exacerbation	9	1	5	3	—
Total	15	1	7	7	—

Good—i.e.—closure of cavities, disappearance of infiltrations, sputum negative in cultures.
Fair—marked diminution of cavities, marked resorption of infiltrations and sputum negative.

TABLE II
INCREASE IN WEIGHT

	Up to 5 Kg.	Up to 10 Kg.	More than 10 Kg.
Fresh tb	1	9	4
Chronic tb	8	4	3
Total	9	13	7

hormones for three to four weeks more enabled us to continue the antimicrobial treatment without disturbances.

At this point we wish to report the following outstanding case: this 57 year old woman, developed a severe allergic rash all over the body, distressingly itching, during antimicrobial treatment. After discontinuation of antibiotics she was given antihistaminic drugs; the rash diminished considerably, but returned in an even more severe form after streptomycin was re-added to the drugs in use. At this point we started on cortisone and before the rash disappeared, streptomycin was again administered, even in daily doses. In spite of this the rash disappeared completely; she continued to receive antibiotics in use in combination with cortisone for another three weeks without side effects, and no side effects were noted even after cortisone was discontinued, while the antibiotics were continued. Similarly good results were achieved in two patients with vertigo after streptomycin administration. In two cases, one with effusion after extra-pleural pneumothorax and one in whom intra-pleural pneumothorax was abandoned, and effusion kept returning after thoraco-centeses and antibiotic treatment, cortisone was started. On two occasions one week apart thoraco-centeses were performed and each time 1 cc. of hydrocorton (25 mg.) were injected into the pleural and extra-pleural spaces respectively. At the same time the patients were given cortisone per mouth, covered by all three antibiotics. The effusion disappeared completely, without relapse. In one case of acute exudative pleurisy with high fever and bad general condition, three liters of serous liquid were aspirated, 1 cc. of hydrocorton was injected and cortisone given per mouth. After one week another 300 cc. of fluid was aspirated and again hydrocorton was injected. The liquid disappeared completely after three weeks and the patient remained with antibiotic treatment only (Figures 1 and 2). It is worth mentioning, that after the first injection of hydrocorton the patient felt great relief, stopped perspiring, the fever decreased to normal within two days, the appetite increased and body weight increased three Kg. weight during the first two weeks. The same course could be observed in the second of the two cases. The effusion disappeared after six days.

In the case of a young Arab girl, tuberculous peritonitis with ascites was diagnosed. Laparotomy was performed in another hospital. For a number of months she was given antimicrobial treatment without effect and aspirations of the fluid had to be done several times on account of reappearance of effusion. She was transferred to our hospital for continuation of treatment where chylous peritonitis was found, apparently due to rupture of a lymph vessel on a tuberculous basis. After one months' treatment with cortisone combined with antibiotics the effusion disappeared completely, and after a few months she was sufficiently recovered to be discharged in good condition.

Two patients, having suffered for years from chronic cavernous pulmonary tuberculosis, had been bedridden for the past few months on

FIGURE 1

FIGURE 2

Figure 1: T. L., 44 years old, male, left tuberculous exudative pleurisy with old fibrotic changes in the left apex. July 1, 1956, Temp. 38.6 (Celsius). *Figure 2:* July 24, 1956 Complete re-expansion of the left lung. Sinus free. Free movements of the left diaphragm.

TABLE III
BACTERIOLOGICAL RESULTS

	B.K. Positive	*B.K. Negative*
Fresh tb:		
Before	12	2
After	3	11
Chronic tb:		
Before	13	2
After	9	6

account of respiratory insufficiency and complete cachexia. In the course of three to four months they were given cortisone, beginning with a daily dose of 100 mg. which was gradually diminished. Their general condition improved greatly, they gained weight, one of them up to 14 Kg. They could walk without breathing difficulties, their general outlook grew more confident; in spite of the fact that radiologically no improvement could be ascertained.

Bacteriologically a sputum conversion of 75 per cent was found in fresh cases after two to three months of treatment which surpasses the percentage that has been achieved after treatment of equal length with antibiotics only (Table III). It is worth noting here that not one of the patients who was negative when treatment was started, converted to positive, neither during nor after termination of treatment.

2. *Radiological Changes:* (Table IV). In patients with pulmonary tuberculosis disappearance or considerable absorption of the exudative changes could be observed following combined treatment with cortisone and antibiotics after shorter periods of time than in patients who received antibiotics only. The most striking absorption was seen in bronchopneumonic or miliaric forms. Interesting to observe was the influence of the

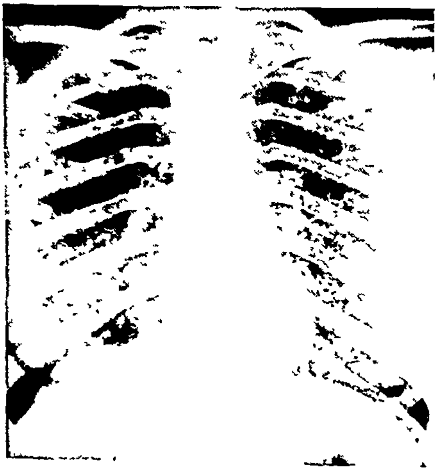

FIGURE 3

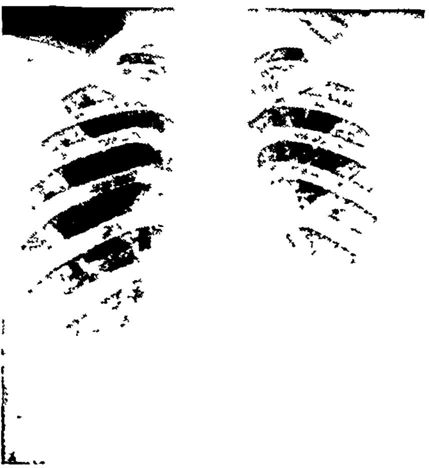

FIGURE 4

Figure 3: Ch. S., 30 years old, female, October 10, 1955, bilateral disseminated tuberculosis. Positive for B.K., Temp. 38.7 (Celsius). *Figure 4:* Ch. S., January 23, 1956, after three months of cortisone treatment: Disappearance of all tuberculous exudative changes. Small fibrotic changes in the left apex.

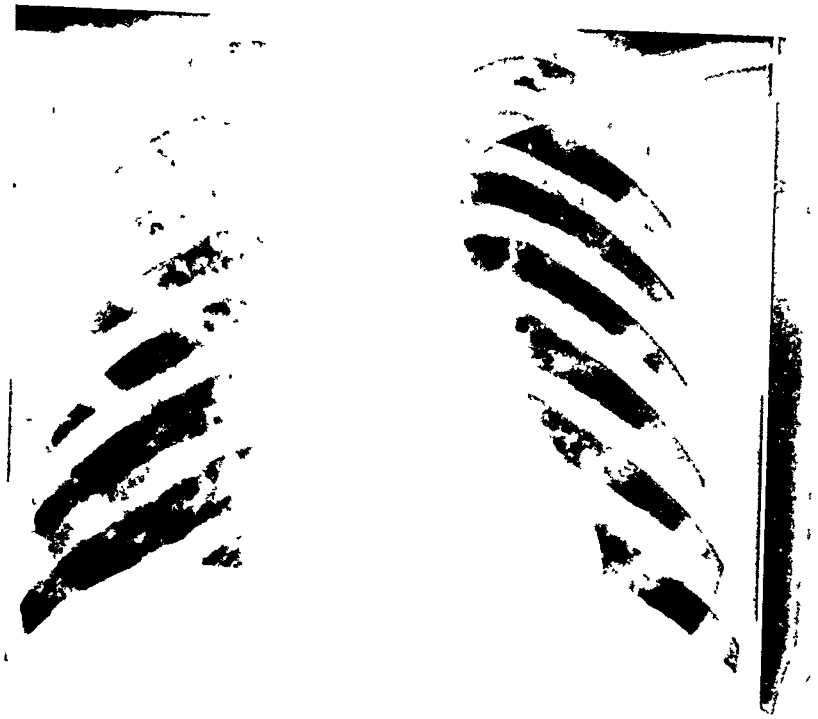

FIGURE 5

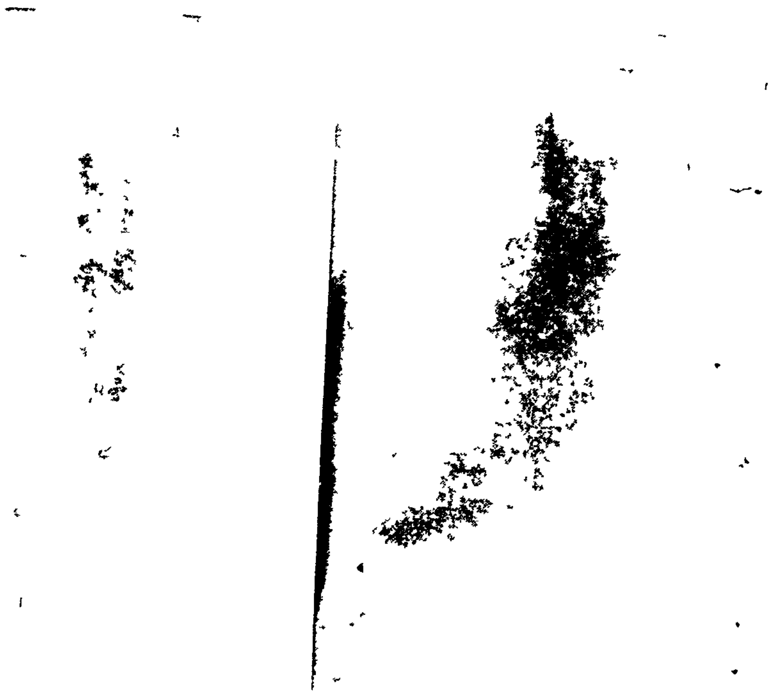

FIGURE 6

Figure 5: M. C., 13 years old, male. October 20, 1955. Right side pulmonary tuberculosis. Infiltrations with cavitations in the right upper lobe. B.K. positive; sedimentation rate 76mm. (Westergren). *Figure 6:* Tomography. Big cavity in the right apex and beyond it a smaller one within exudative process.

TABLE IV
RADIOLOGICAL RESULTS

	Number of Cases	Cured	Improved	No Change	Deteriorated
Fresh tb:					
Nodules or infiltrations	14	8	6	—	—
Cavities	10	6	4	—	—
Chronic tb:					
Nodules or infiltrations	15	—	6	9	—
Cavities	12	1	5	6	—

treatment on different forms of changes, such as nodules, infiltrations, and cavities in fresh and chronic processes. Striking is the fact that the nodules and infiltrations in fresh cases react more promptly to the treatment than the cavities (Figures 3-10). In chronic cases all forms of tuberculous processes react in equal measure to the treatment. The effects of the treatment in fresh cavities were as follows: small cavities closed, big ones either diminished so that only rest cavities remained or were changed into cystic bullae. It is to be emphasized that the results achieved by the hormonal treatment were the same after two or after three months; i.e., that the chief results were reached after two months of treatment (Table V). From the radiological point of view, the administration of the hormones after the first two months is without great value. The percentage of failures grew in direct proportion with the age of the pathological changes. In chronics almost no effect of the hormonal treatment could be observed.

3. *Complications:* As to complications, in only one case did we meet with such severe phenomena as to cause us to discontinue the treatment. In a woman, aged 47, with exudative pulmonary tuberculosis, sugar up to 3 per cent appeared in the urine after one month of treatment with ACTH. At the same time the blood sugar was within normal limits. ACTH was discontinued and after 10 days no more sugar was found in the urine. It is worth noting here that in spite of the appearance of sugar in the urine, the lung condition had improved considerably. In another patient, aged 62, who had received hormone treatment for three and one half months,

TABLE V
COMPARISON BETWEEN RESULTS ACHIEVED BY HORMONAL TREATMENT IN 2 MONTHS AND 3 MONTHS

	Length of Hormonal Treatment	Number of Cases	Cured	Improved
Nodules or infiltrations	2 months	5	3	2
	3 months or more	9	5	4
Cavities	2 months	4	2	2
	3 months or more	6	3	3

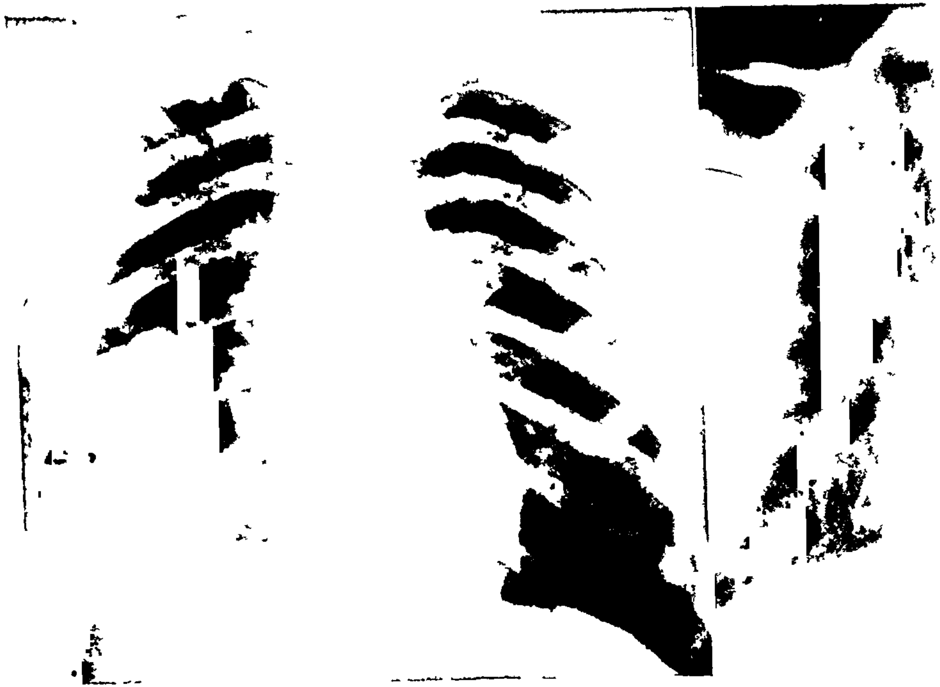

FIGURE 7

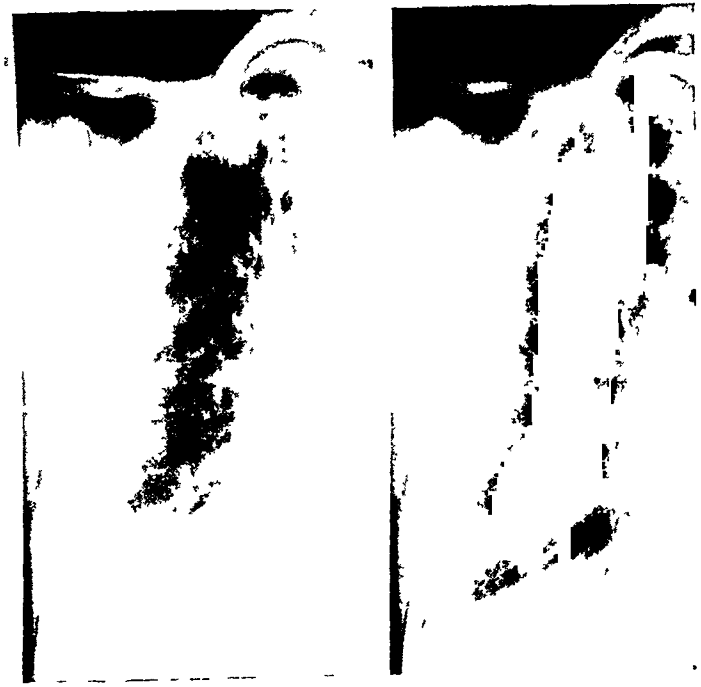

FIGURE 8

Figure 7: M. C., February 14, 1956. After three months of cortisone treatment: closure of cavities; B.K. negative; sedimentation rate 6 mm.; gain in weight 6 Kg. *Figure 8:* Tomography of the same case. No signs of cavitations. Marked resorption of infiltrations.

signs of osteoporosis in the lumbar spine, accompanied by severe pain appeared two months after termination of the treatment. After six weeks' therapy with testosterone, the above described complication disappeared. This case taught us to administer 25 mg. testosterone, one injection per fortnight, to each patient who is given hormones for more than two months. Later on we also found this indication in relative literature.

In a man, aged 29, whose blood pressure had been kept within normal limits (120/85), it suddenly went up to 150/100 in the seventh week of treatment with cortisone. After one weeks' discontinuation of this drug, the blood pressure went down to normal. In a woman, aged 65, with blood pressure 195/80 before initiation of treatment, the blood pressure went up to 270/110 after ten days' treatment with hormones. Two weeks after discontinuation of hormones and administration of reserpine, the blood pressure dropped to 180/80 and remained at this level.

It is also worth putting down that some patients complained of sleeplessness during and mainly at the beginning of treatment. A diminution of the hormone dose always resulted in disappearance of this complaint. In no case did we find changes of the blood electrolytes and in only the one above mentioned sugar was found in the urine. Blood sugar values were always within normal limits. There was no case of psychosis.

Contraindications: Patients suffering from diabetes mellitus, (although here exceptions may be made), hypertension, psychoses, ulcer of the digestive tract, uremia, and degenerative changes of the kidneys should be, in our opinion, considered as contraindicated against treatment with these hormones.

Comment

The papers of Even, Houghton, Spain, Grant, Johnson and Sors on the value and the methods of hormonal treatment in tuberculosis that have

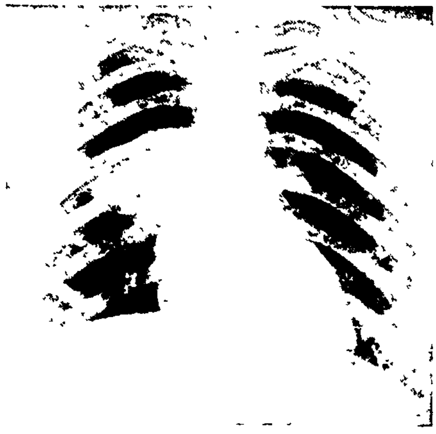

FIGURE 9

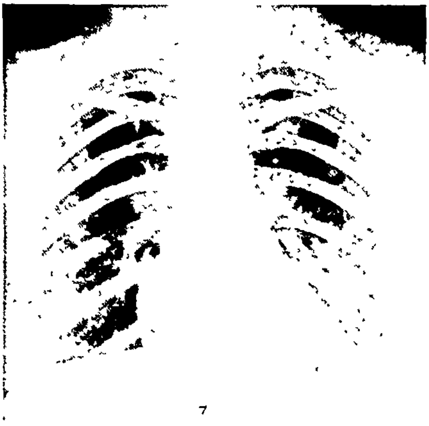

FIGURE 10

Figure 9: L. A., 19 years old, female. January 12, 1956. Big atalectasis in the right middle field. Mantoux: strongly positive; B.K. negative; sedimentation rate: 46mm. (Westergren). Tuberculous inflammation (anatomically proved) of bronchial mucosa in the entrance to the apical segment of the right lower lobe. *Figure 10:* March 20, 1956, after 2 months of treatment with cortisone: clearance of the lung field; B.K. negative; sedimentation rate: 11mm. (Westergren); gain of weight: 10 Kg.

been recently published, try to explain the effect of ACTH and cortisone as causing the disappearance of the exudative changes which, from the histological point of view, are non-specific. In this sense, the effect of the hormones seems more striking and speedy compared to the one achieved by antimicrobial treatment alone. By diminishing the capillary permeability in the inflammatory region, the local oedema and the permeability of cells are diminished. ACTH and cortisone limit and hinder the exudative process without causing growth of fibrous tissue. It seems to us impossible to explain the action of ACTH and cortisone merely by stating its dilatory effect on the inflammatory reaction. Sors and Even express the opinion that ACTH and cortisone limit the action of antibiotics. It may be that this phenomenon results from a freer and easier penetration of Koch bacilli into the tuberculous focus which is not surrounded by perifocal changes. As is well known; antibiotics have, in addition to their bactericidal action, also a direct influence upon the growth of fibrous tissue. The accelerated absorption of the perifocal exudative changes hinders the antibiotics in the organization of fibrosis in this area. Therefore the fibrosis is confined and concentrated in specific changes only. Even is of the opinion that both ACTH and cortisone have a direct influence on the tubercle bacillus. The hormones invigorate its metabolism and influence its growth, in this way they render it more susceptible to the attack of the antibiotics. Of special interest is the opinion of Keller who believes that all the clinical symptoms, appearing in the general condition of the tuberculous patient, including loss of appetite, weakness, cachexia, hypotonia, trouble in the digestive tract, have a close connection with the functional disorders in the adrenals which accompany tuberculosis.

Guiseppe and Bassoli (May, 1955) point out that the elimination of 17-ketosteroids in the urine of tuberculous patients is diminished. This phenomenon is particularly striking in chronic patients. Thus the administration of ACTH and cortisone will improve the impaired function of the adrenals and will influence the tuberculous process.

It appears that as yet there are no sufficient scientific explanations as to the way hormones affect tuberculosis. One thing is certain, that the main influence is the same as in other diseases: anticongestive and antiflogistic effects, in other words, antiexudative and antifibroblastic.

SUMMARY

Twenty-nine cases of pulmonary tuberculosis, of whom 14 were recent, nine were chronic with exacerbation and six were chronic without exacerbation received hormonal treatment, in combination with antimicrobial drugs, during a period varying from two to three months. This treatment was also administered to persons who had pleural fluid asthma, and its complicating tuberculosis.

Cortisone and ACTH can be used safely under antibiotic coverage for the treatment of exudative fresh lesions in pulmonary tuberculosis. Exudative lesions with or without cavitation showed marked improvement compared to treatment without the addition of cortisone—time interval being the same. Identical results pertain to sputum conversion.

Exudative pleurisy and tuberculosis peritonitis improved markedly in a shorter time interval than usual. Chronic pulmonary tuberculosis did not show appreciable x-ray film changes.

In rare cases of respiratory failure and heart failure secondary to cor pulmonale, that did not respond to accepted medical treatment, the addition of cortisone improved the hopeless state.

In cases where antibiotic treatment was not tolerated, addition of cortisone made treatment possible.

The average period of cortisone and ACTH administration in pulmonary tuberculosis was two months. In cases of tuberculous exudative pleurisy treatment was limited to one month. The side effects noted were those of mild and transient glycosuria in isolated cases, mild osteoporosis in one case, and a relative transient elevation of blood pressure in a young man at the termination of treatment. No complication was noted that made interruption of treatment imperative.

RESUMEN

La cortisona y ACTH pueden usarse con seguridad bajo la protección de los antibióticos para las lesiones recientes exudativas de tuberculosis pulmonar. Las lesiones exudativas con o sin excavación mostraron marcada mejoría comparadas con el tratamiento sin la adición de cortisona—siendo el intervalo de tiempo el mismo.

Idénticos resultados se obtuvieron en cuanto a la conversión de los esputos.

La peluresía exudativa y la peritonitis tuberculosa mejoraron marcadamente en período de tiempo más corto que el habitual. La tuberculosis crónica no mostró cambios apreciables a los rayos X.

En raros casos de insuficiencia respiratoria y cardiaca secundaria a cor pulmonale que no respondieron al tratamiento médico usual la adición de cortisona mejoró el estado desesperado.

En casos en que el tratamiento antibiótico no fué tolerado el agregar cortisona hizo posible el tratamiento.

El término medio de tratamiento con cortisona y ACTH en la tuberculosis pulmonar fué de dos meses. En casos de tuberculosis pleural exudativa el tratamiento se redujo a un mes. Los efectos colaterales encontrados fueron una glucosuria moderada y transitoria en casos aislados, osteoporosis y en un caso al final del tratamiento y una elevación relativa temporal de la presión sanguínea.

ZUSAMMENFASSUNG

Cortison und Acth können ohne Gefahr unter antibiotischem Schutz angewandt werden bei der Behandlung frischer exsudativer Herde der Lungentuberkulose. Exsudative Herde mit oder ohne Kavernisierung zeigten ausgeprägte Besserung im Vergleich zur Behandlung ohne Zusatz von Cortison und bei gleichem Zeitabstand. Identische Resultate ergaben sich bezüglich der Entbazillierung des Sputums.

Exsudative Pleuritiden und tuberkulöse Peritonitiden besserten sich deutlich innerhalb kürzerer Intervalle als gewöhnlich. Eine chronische

Lungentuberkulose zeigte keine abschätzbaren röntgenologischen Veränderungen.

In seltenen Fällen von respiratorischem und cardialen Versagen auf Grund eines cor pulmonale, die auf entsprechende interne Behandlung nicht reagierten, besserte der Zusatz von Cortison den hoffnungslosen Zustand. Bei Fällen, in denen die antibiotische Behandlung nicht vertragen wurde, machte der Zusatz von Cortison eine solche Behandlung doch noch möglich. Die Durchschnittsperiode einer Cortison-Acth-Behandlung bei der Lungentuberkulose betrug 2 Monate. Bei Fällen von tuberkulöser exsudativer Pleuritis war die Behandlung auf 1 Monat begrenzt. Die beobachteten Nebenwirkungen bestanden in leichter und vorübergehender Glycosurie in vereinzelten Fällen, leichter Osteoporose in einem Fall und relativ flüchtigen Blutdruckerhöhung bei einem jungen Mann bei Beendigung der Behandlung. Es wurden Komplikationen bemerkt, die die Unterbrechung der Behandlung erforderlich gemacht hätten.

REFERENCES

1 Asby, M. S. and Grant, H.: "Tuberculous Meningitis Treated with Cortisone," *Lancet*, 65-67:6854, 1955.

2 Bassoli, J. De Giuseppe L.: "L'Eliminazione urinaria del 17 Idrossicostricosteroidi come test di funzionalita surrenale in animalati di tuberculosi pulmonare," *Giornale di Medicina e Tisiologia*, 5:513, 1955.

3 Ballario, B. C. and Giovanni, S. Amiza A.: "Topical Hydrocortisone in Pleuropericardial Exudations," *Diseases of the Chest*, 27:190, 1955.

4 Even, R. et Sors, Ch.: "Treatment precoce de la meningite tuberculeuse par antibiotiques et ACTH," *Review de la Tuberculose*, 19:171, 1955.

5 Ebert, Robert H.: "In Vivo Observations of the Effect of Cortisone on Experimental Tuberculosis, Using the Rabbit Ear Chamber Technique," *Am. Rev. Tuberc.* 64-65, 1952.

6 Even, R., Sors, Ch., Delaude, A., Roujeau, J., Trocmé, Y. and Commare, G.: "La place des hormones hypophyso surrenales dans le traitement de la tuberculose," *Revue de la Tuberc.*, 12:1250, 1955.

7 Houghton, L. E. and Davies, D.: "The Effect of Cortisone on B.C.G. Vaccination in Guinea Pigs," *Tucercle*, 1:2, 1954.

8 Houghton, L. E.: "Combined Corticotropin Therapy and Chemotherapy in Pulmonary Tuberculosis," *Lancet*, 266:595, 1954.

9 Johnson, R. and Winthrop, N. D.: "Cortisone, Corticotropin and Antimicrobial Therapy in Animal and Men," *Am. Rev. Tuberc.* 70:623, 1954.

10 Keller, N. S. and Heizman, R.: "17 Ketosteroid—und Vitamin C.—Ausscheidung bei Lungentuberculose," *Beitr. Klin. Tuberc.*, 112.3:222, 1954.

11 Lurie, M. B., Zappasodi ä. Danenberg, A. M. and Cordona-Lynch, E.: "The Effect of Cortisone and ACTH on the Pathogenesis of Tuberculosis," *The Annals of the New York Academy of Science*, 56:779, 1952.

12 Linquette, M., Goudemand, M. and Warot, P.: "L'action de la cortisone sur les exudats de sereuses," *Presse med.*, 62:168, 1954.

13 Spink, W.: "Adrenocorticotropic Hormone and Adrenal Steroids in the Management of Infectious Diseases," *Ann. Int. Med.*, 10:685, 1955.

14 Spain, D. M. and Molomut, N.: "Effects of Cortisone in the Development of Tuberculous Lesions in Guinea Pigs and on Their Modifications by Streptomycin Therapy," *Am. Rev. Tuberc.*, 62:337, 1950.

15 Spain, D. M.: "Some Basic Biologic Effects of Cortisone as Related to Pulmonary Diseases," *Dis. Chest*, 23:270, 1953.

16 Sors, C. and Trocme, J.: "Le traitement der pleuresies sero-fibrineuses. Tuberculeuses par L'ACTH," *Rev. de la Tuberc.*, 18:167, 1954.

17 Winner, H. J. and Evans, W. E.: "Experimental Tuberculosis in Cortisone Treated Guinea Pig," *Tubercle*, 23:239, 1952.

SECTION ON CARDIOVASCULAR DISEASES

Pulmonic Valvular Stenosis Associated with Interatrial Septal Defects

J. L. EHRENHAFT, M.D., F.C.C.P., E. O. THEILEN, M.D.
and MONTAGUE S. LAWRENCE, M.D.
Iowa City, Iowa

Clinical investigation and surgical treatment of patients with valvular pulmonic stenosis and with atrial septal defects has shown frequent coexistence of the two lesions. These associated anomalies were encountered 12 times in a series of 50 patients with atrial septal defects. This group also constituted approximately 25 per cent of the patients operated upon for valvular pulmonic stenosis with intact ventricular septum. This presentation summarizes our experience with this particular combination of lesions.

Valvular pulmonic stenosis with a right to left shunt at the atrial level is the second most common cause of cyanotic congenital heart disease. The existence of left to right interatrial shunts without arterial oxygen desaturation in the presence of pulmonic stenosis is also well recognized. Several reports have suggested that right to left interatrial shunts may be secondary to increases in right atrial pressure which permit flow through a probe patent foramen ovale or that the shunt is the result of dilatation of the foramen ovale. It has been suggested that many of these communications in the septum are not true atrial defects. In patients with left to right shunts the opinion has been expressed that the pressure gradient across the pulmonary valve may often be the result of a functional stenosis rather than of true pulmonary outflow tract obstruction. In this series of 12 patients with diagnoses verified at open cardiotomy, the pulmonic valves were malformed in every instance and produced significant obstruction. In each instance the atrial septal defect was an open communication between the atria rather than a probe patent foramen ovale. All the defects were of the ostium secundum type. Some of them were fenestrated and others had the appearance of a greatly dilated foramen ovale.

The age range of these patients was three and one half to 30 years. Eight of the 12 were females. Growth and development were abnormal in seven

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From the Departments of Surgery and Medicine, State University of Iowa, College of Medicine.

who were more than one standard deviation below the mean values for height and weight for their ages. Growth and development had no clear-cut relationship either to the severity of the pulmonic stenosis or to the size and direction of the atrial shunts.

The symptoms of these patients were fatigue and decreased exercise tolerance manifested primarily by shortness of breath on exertion. Severe chronic cardiac failure was present in the oldest patient in the series. One child had a history of syncopal episodes. He had a relatively mild pulmonic stenosis and was intermittently cyanotic. Whether or not the syncope was related to the cardiac lesions is questionable. Constant cyanosis was present in three patients and according to the history had been life-long in two. Four had a history of intermittent cyanosis related to exertion. Two of these at the time of cardiac catheterization had evidence of reduced peripheral arterial saturation at rest. The other two had predominant left to right interatrial shunts with normal peripheral arterial saturation at rest. Squatting was observed in two patients only. In the patients with predominant right to left shunts the history of slow progression of the cyanosis over a long period of time was obtained.

Physical findings were dominated by signs of pulmonic stenosis. In those patients with right to left shunts it was often possible to differentiate this lesion from the tetralogy of Fallot on the basis of auscultatory findings. Characteristically a loud harsh systolic murmur of medium pitch lasting throughout systole was maximal in the second and third left intercostal spaces at the parasternal line. The murmur often radiated toward the left shoulder at the level of the second interspace. The first heart sound in the second interspace was frequently accentuated and had a "snapping" or "booming" quality. The second sound when audible was diminished. In a few instances it was clearly split. The three patients who were cyanotic at rest had clubbing of the fingers and toes.

Electrocardiographic changes of right ventricular hypertrophy were present in eight patients. These consisted of monophasic QRS complexes with tall R waves and delayed intrinsicoid deflections, depressed S-T segments and inverted T waves in precordial leads subtending the right ventricle. These changes were compatible with so-called systolic overload of the right ventricle. The changes of both incomplete right bundle branch block and right ventricular hypertrophy occurred three times. The right ventricular pressures in these patients were 40, 48 and 58 mm. Hg. Only one patient with relatively mild pulmonic stenosis showed an incomplete right bundle branch block. Her right ventricular pressure was 45 mm. Hg.; her pulmonary artery pressure was 23/13. An atrial septal defect with a large left to right shunt was the predominant lesion. Three patients with predominant right to left shunts showed P wave abnormalities consisting of tall, narrow peaked deflections. Their right atrial pressures were elevated and ranged from 10/3 to 16/6 mm. Hg.

Radiographic examination including cardiac fluoroscopy was helpful in establishing the diagnosis when post-stenotic dilatation of the pulmonary artery could be demonstrated. In the cyanotic patients right to left interatrial shunts occasionally could be demonstrated by angiocardiography (Fig. 1). The vascular markings were not particularly indicative of reduced pulmonary flow, even when rather severe stenosis was present. They were definitely decreased in only two patients. On the other hand, the markings were not significantly increased except in one who had a large left to right shunt (59 per cent of total left atrial flow). A concave midsegment in the postero-anterior projection associated with elevation of the apex of the heart was seen in four patients and suggested the possibility of infundibular rather than valvular stenosis. Both cardiac catheterization and later cardiotomy demonstrated that the stenosis was valvular.

Cardiac catheterization was done in all of these patients. Four of the children were sedated either with morphine and scopolamine or with a small amount of rectal pentothal. The Van Slyke method was used to estimate blood oxygen content. In addition to determining arterial oxygen saturation at rest and while breathing room air, oxygen content was

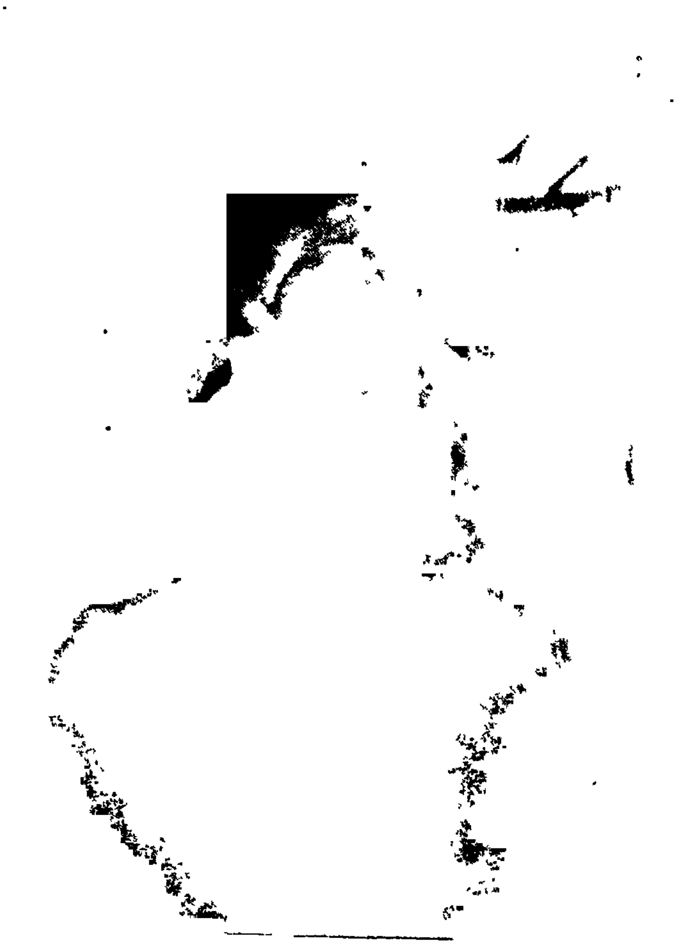

FIGURE 1: Angiocardiogram of a cyanotic patient demonstrating the right to left interatrial shunt and the poststenotic pulmonary artery dilatation.

also measured after the patient breathed 100 per cent oxygen for 10 minutes. With this technique blood is normally 100 per cent saturated with oxygen, and in addition 2.0 volumes per cent of oxygen are dissolved in the plasma. The error is approximately ± 0.5 volumes per cent. Normal values preclude a right to left intracardiac shunt.

The patients are divided into two groups according to whether the shunts were predominantly left to right or right to left. The shunt was predominantly right to left in five (Group I—Table I) and left to right in seven (Group II—Table II). Three of the five with right to left shunts (Group I) were definitely cyanotic; the other two were not obviously cyanotic at rest but had reduced arterial oxygen saturations. Right to left shunts varied from 20 to 40 per cent of total right atrial flow. Cardiac catheterization in Group I did not demonstrate significant increases in arterial oxygen content of the right atrial samples compared with vena caval samples. Right ventricular systolic pressures exceeded the systemic arterial systolic pressure in three patients by 30 to 90 mm. Hg. This was a helpful point in concluding that the ventricular septum was intact. Right ventricular end-diastolic pressures were elevated in four of the five with right to left shunts. Five of seven with left to right shunts also had some elevation of right ventricular end-diastolic pressures.

Two with right to left shunts including one with an arterial oxygen saturation of only 80 per cent had normal pulmonary artery pressures. The other three in the group with right to left shunts had abnormally low pul-

TABLE I

PREOPERATIVE CATHETERIZATION DATA OF 5 PATIENTS WITH PREDOMINANTLY RIGHT TO LEFT SHUNTS

		Pressures mm. Hg.									
	AGE+SEX	SYST.	R.V.	P.A.		SYST. GRAD.	ATRIAL		ART. O_2 SAT. %		SIZE ATRIAL DEFECT
				Syst./Dia.	Mean		R.A.	L.A.	Room air	100% O_2	
B.L. 53-1246	7 ♀	102/5/15 *	65/10	20/12	14	45	16/6 (12)	15/4	80	94	2 cm
V.N. 56-229	12 ♀	115/60	58/8	26/13	17	32	10/3 (5)	11/2	91	100+ 08vol%	2 cm
D.W. 55-4323	13 ♂	125/65	155/5	12/7		143	13/2 (5)	13/3 (6)	86		2 cm
C.D. 56-5719	28 ♂	120/75	150/8	17/3	10	133	12/4 (8)	9/5 (7)	86	95	3 cm
M.W. 49-10381	30 ♀	100/60	190/10	15/5		175	12/2 (6)	12/2 (6)	82		5 cm

( ) = mean pressures
* = left ventricular pressures

monary artery pressures. They were also the ones with the highest right ventricular pressures and had systolic gradients between the right ventricle and the pulmonary artery ranging from 133 to 175 mm. Hg.

Three children with definite valvular pulmonic stenosis but with left to right shunts varying from 50 to 66 per cent of total left atrial flow had only moderate elevation of right ventricular pressures and normal pulmonary artery pressures. Three others in the same group with systolic gradients between the pulmonary artery and right ventricle of 71 to 78 mm. Hg. had pulmonary artery pressures slightly less than normal for their age but still shunted from left to right. The volume of the shunt was reduced however, and ranged from 18 to 41 per cent of total left atrial flow. An arterial saturation of 94 per cent was obtained in one of these patients (L. C.). The sample after breathing 100 per cent oxygen was lost. There is therefore the possibility that she might have had a bidirectional shunt.

It was possible to catheterize the left atrium in nine of the 12 patients of this series. Right atrial pressure was greater than left atrial pressure in two with right to left shunts; in three others with right to left shunts right and left atrial pressures were essentially the same although both were higher than normal. Left atrial pressure exceeded right atrial pressure in three with left to right shunts and was essentially the same in one. The differences in most of the atrial pressure measurements were relatively

TABLE II
PREOPERATIVE CATHETERIZATION DATA OF 7 PATIENTS WITH PREDOMINANTLY LEFT TO RIGHT SHUNTS

		Pressures mm. Hg.										
	AGE+SEX	SYST.	R.V.	P.A.		SYST. GRAD.	ATRIAL		ART. O_2 SAT. %		SHUNT %L.A. FLOW	SIZE ATRIAL DEFECT
				Syst./Dia.	Mean		R.A.	L.A.	Room air	100% O_2		
R.S. 54-10634	3 ♂		37/6	17/9	12	20	9/4 (6)	11/5	96		16	2 cm.
D.H. 55-9005	5 ♀	100/72	88/8	17/13	14	71	11/6 (9)	17/10*	96	100 + 1.8 vol.%	18	1 cm.
J.B. 54-7104	7 ♀	110/70	48/8	20/9	13	28	8/4 (5)		99	100 + 2.2 vol.%	50	3.5 cm.
R.L. 54-14779	7 ♀	95/65	40/7	20/11	14	20	7/4 (5)	8/3 (5)	95	100 + 0.6 vol.%	59	2 cm.
R.S. 56-9537	10 ♀	125/75	45/8	23/13	16	22	9/3 (6)	15/7 (11)	97	100+ 2 vol.%	66	2.5 cm.
G.P. 44-1405	18 ♂	120/75	95/8	23/4	15	72	6/2 (3)		100	100 + 1.6 vol%	40	2.5 cm.
L.C. 56-16970	22 ♀	143/77	98/10	20/8	11	78	10/4 (6)		94		41	2.5 cm.

( )= mean pressures
* = pulm vein

small and in some instances may not be particularly significant.

The aim of surgical treatment must be obliteration of the shunt between the atria and the reduction of the gradient between the right ventricular and pulmonary artery pressures. Pulmonary valvulotomy and closure of the atrial septal defects were accomplished in all of these patients. In our opinion direct visual control in a bloodless operative field, as in all other types of surgery, is essential for the correction of the defects with optimum results. We have found the use of generalized body hypothermia most satisfactory in the management of these patients. Inflow and outflow tract occlusion of the large vessels with temporary exclusion of the heart permits the direct approach to the stenotic pulmonic valve. During a second period of occlusion right auriculotomy and closure of the atrial septal defect can easily be carried out (Fig. 2). Eleven of the 12 patients were prepared for open cardiotomy by this method while one was placed on the extracorporeal circuit and pump oxygenator for repair of the defects. This one was thought to have an additional interventricular septal defect. This, however, was not verified at operation. Uniformly, the pulmonic stenosis encountered was of the valvular type. The stenosis was formed by fusion of three semilunar valves into a cone-shaped structure that produced vary-

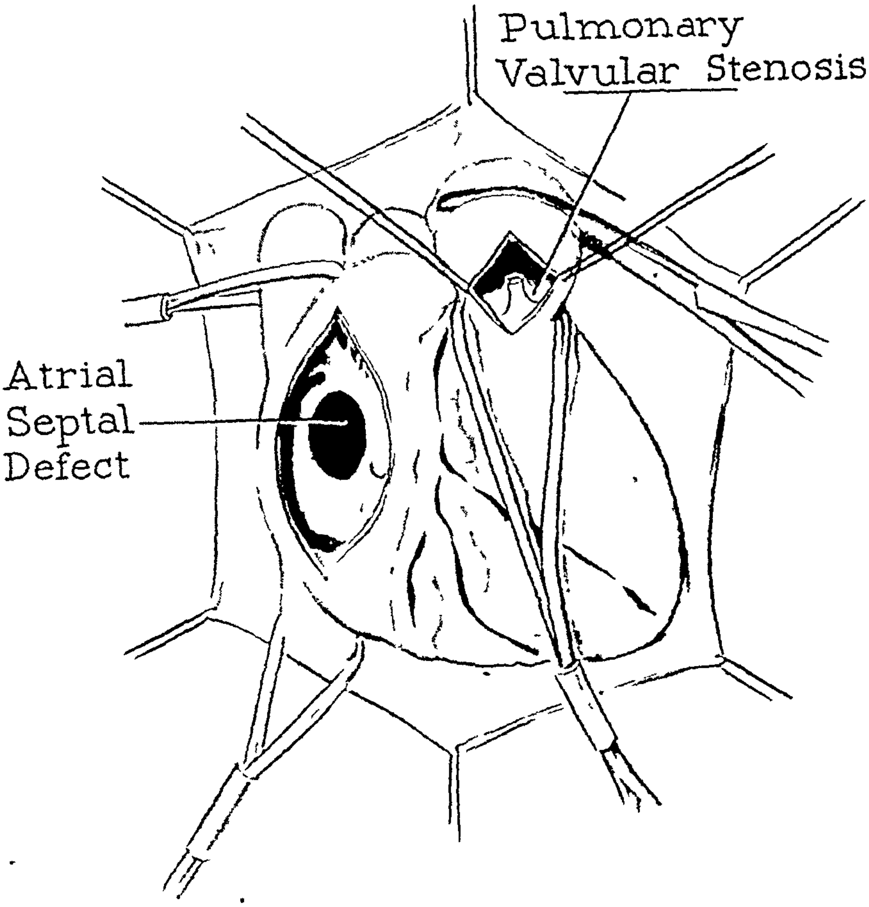

FIGURE 2: Schematic drawing showing the interatrial septal defect and the pulmonic valvular stenosis.

ing degrees of right ventricular outflow tract obstruction. Associated muscular infundibular stenosis was not observed in any of the patients even though the right ventricular outflow tract may have been narrowed in some of the patients by the severe concentric muscular hypertrophy. This occurred most frequently in the patients with arterial oxygen desaturation and very high right ventricular pressures. In no instance could the obstruction of the right ventricular outflow tract be classified as a "relative" one. Moderate to severe post-stenotic pulmonary artery dilatation was found in all patients with low or normal pulmonary artery pressures.

The interatrial septal defects were all of the ostium secundum type. The diameters varied from 1 cm. to 5 cm. We believe that most of the defects resulted from dilatation of the foramen ovale. In all instances there was free communication between the atria permitting shunts in either direction. It is inconceivable that defects of this size and type could close spontaneously after correction of the pulmonic valvular stenosis. Pulmonic valvuloplasty alone could produce some improvement in patients with right to left shunts but in others with predominant left to right shunts an increase in the volume of the shunt could occur that would make a second operative procedure necessary.

There has been no death in this series. Generally the postoperative courses were uncomplicated. In patients with large interatrial septal defects and left to right shunts mild pulmonic stenosis may be beneficial in protecting the pulmonary arterial tree from secondary degenerative change as a result of increased pulmonary flow. This may be a factor in the low mortality associated with the surgical correction of both defects. Preoperative cyanosis was relieved. Clubbing and polycythemia have disappeared. In some of these patients, as in others with isolated valvular pulmonic stenosis studied by cardiac catheterization after pulmonary valvulotomy, a systolic pulmonic murmur may persist for a time. The pressure gradients between the right ventricle and pulmonary artery in most of them have disappeared or have been markedly reduced. Despite a complete pulmonary valvulotomy the post-stenotic pulmonary artery dilatation does persist. The murmur usually diminishes in intensity with the passage of time. Possibly this may be related to a gradual decrease of the ejectile force of the hypertrophied right ventricle postoperatively.

SUMMARY

Twelve patients with valvular pulmonic stenosis and either right to left or left to right interatrial shunts have been reported. The direction and volume of the interatrial shunt is ultimately a function of the severity of the valvular pulmonic stenosis. Both defects were corrected in all of these patients by open cardiotomy, using hypothermia in 11 and a pump oxygenator in one. There were no deaths. Since the most common associated defect in patients with valvular pulmonic stenosis is an atrial septal defect, atrial exploration is indicated in all patients undergoing surgery for valvular pulmonic stenosis. A method should be used which will permit correction of both defects at the same operation by open cardiotomy.

RESUMEN

Se presentan doce enfermos con estenosis pulmonar valvular y con communicaciones interatriales ya de derecha a izquierda oinversas. La dirección y volumen de las intercommunicaciones atriales es en último análisis en función de la severidad de la estenosis valvular pulmonar. Ambos defectos fueron corregidos en todos estos enfermos mediante cardiotomía abierta, usando hipotermia en once y oxigenador de bomba en uno.

No hubo muertes. Puesto que el defecto más común que se asocia con la estenosis valvular pulmonar es el defecto septalatrial, la exploración atrial está indicada en todos los enfermos que se someten a la cirugía por estenosis valvular pulmonar. Debe usarse un método que permita la corrección de ambos defectos durante la misma operación por cardiotomía abierta.

ZUSAMMENFASSUNG

Es wird berichtet über 12 Patienten mit pulmonaler Klappenstenose und intraatrialem Rechts-Links- oder Links-Rechts-Shunt. Die Richtung und das Ausmass des interatrialen Shunts sind letzten Endes eine Funktion der Schwere der pulmonalen Klappenstenose. Beide Schäden wurden bei sämtlichen Patienten mittels offener Cardiotomie behoben und zwar unter Anwendung der Unterkühlung bei 11 Kranken und einer Pumpe und Oxygenator bei einem Kranken. Todesfälle kamen nicht vor. Da der am häufigsten bei Kranken mit pulmonalen Klappenstenosen gemeinsam damit vorkommende Fehler in einem Vorhofs-Septum-Defekt besteht, ist eine Untersuchung des Vorhofes bei allen Kranken angezeigt, bei denen ein Eingriff wegen pulmonaler Klappenstenose vorgenommen wird. Man muss sich einer Methode bedienen, die eine Behebung beider Schäden durch dieselbe Operation und mittels offener Cardiotomie ermöglicht.

BIBLIOGRAPHY

Abrams, D. G. and Wood P.: "Pulmonary Stenosis with Normal Aortic Root," *Brit. Heart J.*, 13:519, 1951.

Engle, M. A. and Taussig, H. B.: "Valvular Pulmonic Stenosis with Intact Ventricular Septum and Patent Foramen Ovale. Report of Illustrative Cases and Analysis of Clinical Syndrome," *Circulation*, 2:481, 1950.

Magidson, O., Cosby, R. S., Dimitroff, S. P., Levinson, D. C. and Griffith, G. C.: "Pulmonary Stenosis with Left to Right Shunt," *Am. J. Med.*, 17:311, 1954.

Rudolph, A. M., Nadas, A. S. and Goodale, W. T.: "Intracardiac Left to Right Shunt with Pulmonic Stenosis," *Am. Heart J.*, 48:808, 1954.

Selzer, C. and Carnes, W. H.: "The Role of Pulmonary Stenosis in the Production of Chronic Cyanosis," *Am. Heart J.*, 45:382, 1953.

Swan, H. and Blount, S. G.: "Visual Intracardiac Surgery in a Series of One Hundred Eleven Patients," *J.A.M.A.*, 162:941, 1956.

Voegelpoel, L. and Schrire, V.: "The Role of Auscultation in the Differentiation of Fallot's Tetralogy from Severe Pulmonary Stenosis with Intact Ventricular Septum and Right to Left Interatrial Shunt," *Circulation*, 11:714, 1955.

The Hemodynamic and Clinical Characteristics of Rheumatic Aortic Stenosis

H. GOLDBERG, M.D., F.C.C.P., C. DENTON, M.D., S. BENDER, M.D.*
and J. URICCHIO, M.D., F.C.C.P.
Philadelphia, Pennsylvania

The recent advances in the surgical treatment of aortic stenosis[1] have necessitated a more precise evaluation of the disease, especially with regard to its severity in any given patient. Clinical judgment of severity has been based on certain well-defined symptoms and signs.[2, 3] Whether this judgment is adequate to assess the patient as a candidate for surgery is by no means certain.[4] Left heart catheterization provides a method for defining the physiologic significance of the obstruction at the aortic valve, by measuring the pressure gradient across the valve during systole.[5 6] When this information is combined with a flow measurement, estimated by simultaneous right heart catheterization, the degree of stenosis can be defined more accurately than previously.[7]

The purpose of this paper is to present the clinical and physiologic data from a group of patients with aortic stenosis, and attempt a correlation of these findings.

Material

Forty-five patients with clinically identifiable aortic stenosis and no other valvular lesion were selected for this study. In 41, the lesion was believed to be rheumatic, although only 10 had a clear-cut history of rheumatic activity in the past, while in four it was on a congenital basis. Forty of the patients were men; five women. The age range of the group was 14 to 62 years. In 39 cases transaortic commissurotomy was performed and the surgeon's description** of the valve confirmed the presence of a tight stenotic lesion.

Method

History, physical examination, electrocardiogram, and cardiac x-ray film and fluoroscopy studies in postero-anterior, oblique and lateral views with barium swallow, were obtained in all cases. Simultaneous catheterization of the right and left sides of the heart was performed in all patients in the post-absorptive state. Although some patients had a history of congestive failure, no patient was judged to be in failure at the time of the study.

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From the Brith Sholom Cardiopulmonary Laboratory and Department of Medicine, Hahnemann Medical College and Hospital, Bailey Thoracic Clinic.

*Work done during tenure of a Public Health Research Fellowship.

**All cases were operated upon by Drs. Charles P. Bailey, Henry T. Nichols, and/or Houck Bolton.

Premedication consisted of 200 mgm. of seconal and 50 mgm. of demerol. Any patient who had been taking digitalis was continued on this drug.

Although a detailed accounting of the procedure may be found elsewhere,[7] a brief resume will give a clearer understanding of the way in which the information is obtained. Right heart catheterization was performed in the usual way. After the catheter had been wedged to measure the pulmonary capillary pressure, it was withdrawn to the pulmonary artery and left there while the patient was turned to the prone position. A Cournand needle was placed in the brachial artery. A six inch thin-walled 18 gauge needle was then introduced, through the eighth or ninth right intercostal space near the spine, into the left atrium, according to the Fisher modification[8] of the Bjork technique.[9] A polyethylene catheter was inserted through the needle into the atrium, advanced to the left ventricle, and occasionally out to the aorta. At this point all manipulation was halted. When the heart rate, rhythm and blood pressure were stable, expired air was collected in a Tissot spirometer for three minutes, and during this period simultaneous pulmonary artery and brachial artery blood samples were withdrawn. Then pressures were recorded from the left ventricle and brachial artery simultaneously, so that the pressure gradient across the aortic valve could be measured. Pressures were then recorded as the left heart catheter was withdrawn from the ventricle to the atrium. Whenever the catheter was advanced as far as the aorta, it was withdrawn to the ventricle, so that a "pull-back" gradient could be measured and compared with the simultaneous left ventricular brachial artery gradient.

Pressure recordings were made in some of the patients by electromanometers (Sanborn) on a direct writing recorder (Sanborn). In later pa-

TABLE I
SUMMARY OF PHYSIOLOGIC DATA

	Normal	Aortic Stenosis
1. Cardiac Index (1/m/M^2)	2.6-3.6	1.2-4.4 (2.8)
2. Aortic Valve Flow cc./S.E.P. sec.)	175-250	70-317 (166)
3. L. V. Mean Systolic Ejection Pressure (mm. Hg.)	70-126	140-260 (199)
4. L.V.-B.A. Pressure Gradient (mm. Hg.)	—30 to +2	+28 to +153 (+76)
5. Aortic Valve Area ($cm.^2$)	3.0	0.2-1.2 (0.5)
6. L.V. Total Work (Kg. M/min.)	2.9-3.9	2.4-10.1 (5.5)
7. L.V. End Diastolic Pressure (mm. Hg.)	10	0-44 (16)
8. L.A. Mean Pressure (mm. Hg.)	4-10	0-35 (12)
9. P.A. Mean Pressure (mm. Hg.)	20	8-56 (22)
10. Pulmonary Vascular Resistance (dynes/sec./$cm.^{-5}$)	200	22-1050 (251)

tients in the group, a p-23D Statham strain gauge was used in conjunction with a photographic six-channel recorder (Electronics for Medicine). With the latter one can record several pressures with gauges of equal sensitivity simultaneously on a common baseline.[10] The zero level for pressure was taken as 5 cm. below the angle of Louis.

Blood oxygen was determined by the method of van Slyke and Neil. Oxygen content of the expired air was measured with the Pauling Oxygen Analyzer. The cardiac output was calculated by the direct Fick method. Pressure gradients were measured by planimetric integration of the area between the left ventricular and brachial artery pressure curves; tracings of the curves were superimposed for this purpose when the recordings were not on a common baseline (Sanborn recorder). Valve flow and area, pulmonary resistance, and ventricular work were calculated by modification of the formulae of Gorlin and Gorlin.[11]

$$\text{A. V. F. (cc./S. E. P. sec.)} = \frac{\text{C. O.}}{\text{S. E. P. x H.R.}}$$

$$\text{A. V. A. (cm.}^{2}\text{)} = \frac{\text{A. V. F.}}{44.5\ (\text{L. V.}_{\text{SM}}\text{—B. A. or A. O.}_{\text{SM}})}$$

$$\text{P. V. R. dynes. sec. cm.}^{-5}\text{)} = \frac{(\text{P. A. m.—L. A. m})\ \text{x}\ 1332}{\text{C. O. (m.l/sec.)}}$$

$$\underset{\text{t. w.}}{\text{L. V. (Kg.M/min.)}} = \frac{(\text{C. I. x } 1.055)\ (\text{L. V. s.m. x } 13.6)}{1000}$$

A. V. F. = aortic valve flow =

S. E. P. (sec.) = systolic ejection period

C. O. = cardiac output (l./min.)

H. R. = heart rate per minute

A. V. A. = aortic valve area

L. V. = mean systolic ejection pressure of the left ventricle

s. m.

B. A. (orA)

s. m. = mean systolic brachial artery or aortic pressure

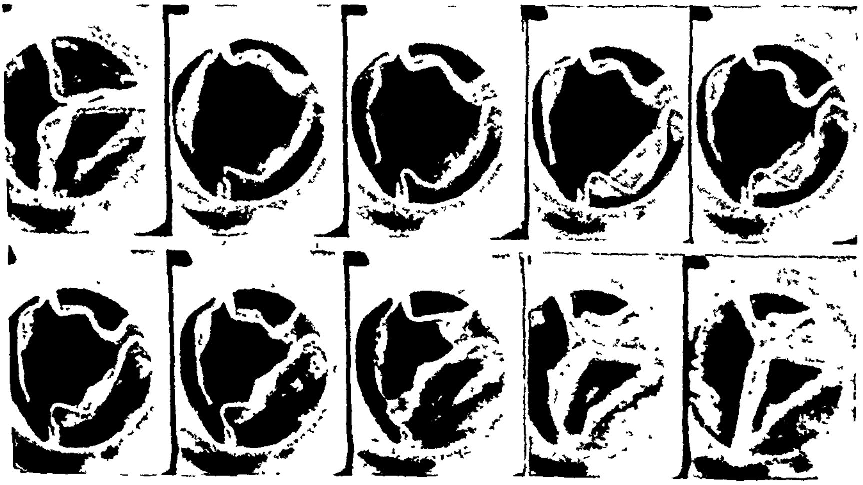


FIGURE 1A: Cinematophotograph of a perfusion of a normal aortic valve. Note size of valve orifice at height of systole in insert 3rd from left. (Top) (Courtesy I. K. R. Macmillan, British Heart Journal Vol. 17, p. 56).

P. V. R. = pulmonary vascular resistance (dynes/sec./cm.$^{-5}$)

L. V.$_{t.w.}$ = total left ventricular work

P. A.$_m$ = mean pulmonary artery pressure

L. A.$_m$ = mean left atrial pressure

C. I. = cardiac index (L./min./M^2)

An evaluation was made of a number of cardiac clinical symptoms and signs, independently of knowledge of the catheterization figures. An attempt was made to grade (basis 0 to 4) the murmurs and the symptoms of dyspnea, angina and syncope.

Results

The normal physiologic findings and those found in our cases of aortic stenosis are summarized in Table I.

The cardiac index and the aortic valve flows tend to be below normal for the group as a whole. The former average 2.81/m/m^2 with a range of 1.2 to 4.4, while the aortic valve flows average 166 cc./S.E.P., with a range of 70 to 317.

In an individual with a normal aortic valve, the aortic and left ventricular pressures are practically identical during ejection (Fig. 1). In aortic stenosis, the ventricular systolic pressure is consistently elevated and greater than the aortic (or brachial artery) systolic pressure. This gradient of pressure is the constant physiologic abnormality in aortic stenosis, ranging between 28 and 153 mm. Hg. in this series (Fig. 2).

The aortic valve areas were greatly reduced, falling below 1.2 cm.,^{2} and

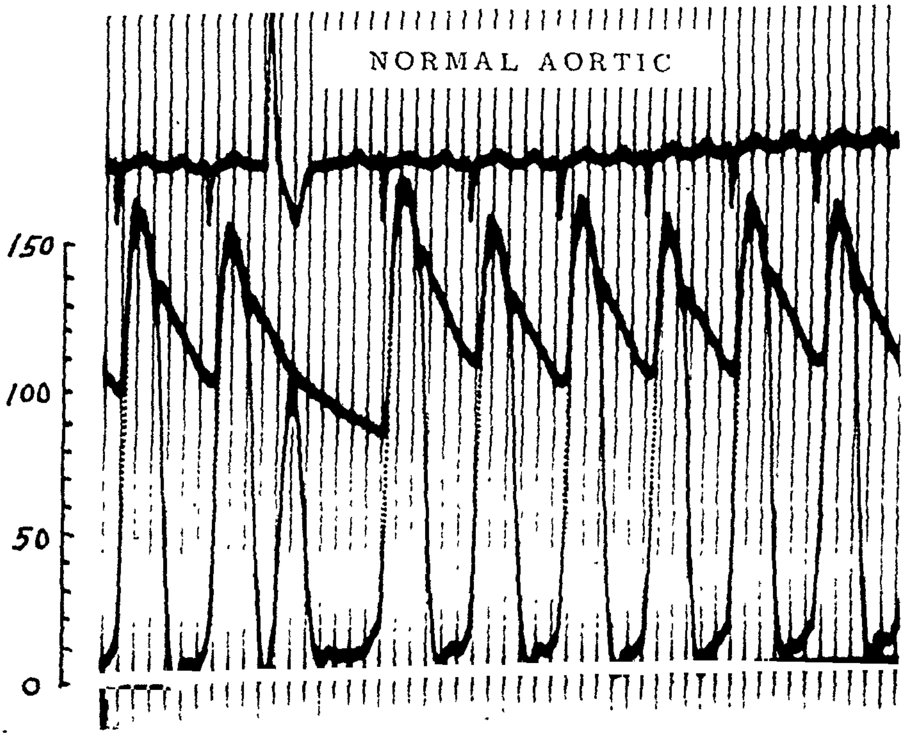


FIGURE 1B: Left ventricular and aortic pressure tracings simultaneously recorded in an individual with a normal aortic valve. Note identical pressures during the systolic ejection period.

TABLE II
AORTIC STENOSIS (45) CASES—PHYSICAL FINDINGS

Aortic Murmurs	
Systolic	45
Diastolic	15
Aortic Second Sound	
Absent	26
Diminished	17
Normal	2

averaging 0.5 cm.^{2} for the group. This represents $\frac{1}{6}$ of the estimated normal aortic valve area of 3.0 cm.^{2}

Total left ventricular work was generally increased up to two to three times normal. In several patients it was low or within normal limits, despite severe obstruction due to a marked reduction in the cardiac index.

Patients with aortic stenosis show an abnormal physiologic response to exercise. As reported previously[12] there is frequently an inadequate rise in the cardiac output during stress (Fig. 3). The pressure gradient and flow across the valve may or may not increase. The stroke of work of the left ventricle hence may change only slightly, certainly less than in the normal individual performing the same exertion as judged by the oxygen consumption (Fig. 4).

The left ventricular diastolic pressure was elevated above the normal of 10 mm. Hg. in 25 patients, being as high as 44 mm. Hg. The left atrial pressure reflected this elevation, particularly at the end of diastole in a giant "a" wave.

In 12 patients the pulmonary artery pressure was moderately elevated. Pulmonary hypertension was observed in four of the six cases who were in heart failure at the time of admission, although catheterized at a time when they were judged no longer in failure, and in an additional eight of 11 cases who gave a history of failure in the past. In these patients elevations of the pulmonary vascular resistance were observed.

We are not presenting in this paper any of the results of our analysis of the severity of clinical symptoms on a graded basis. This analysis was performed for the purpose of trying to correlate the symptoms and the physiologic data. No such correlation was obtained, with single symptoms and single physiologic parameters, or combinations of each. Since this was the only purpose of the grading, the presentation of the statistics on the number of patients with each grade of each symptom would be of no value.

Exertional dyspnea was the most frequent cardiac complaint, occurring in 78 per cent of the cases (Fig. 5). Nocturnal dyspnea occurred in six patients. Angina, classically precipitated by exertion with or without typical radiation, appeared in 24 (56 per cent). Syncope or vertigo was a complaint in 40 per cent. Eleven patients gave a history of failure in the past.

On physical examination all had a harsh aortic systolic murmur. A faint diastolic murmur was heard in 15. The second aortic sound was

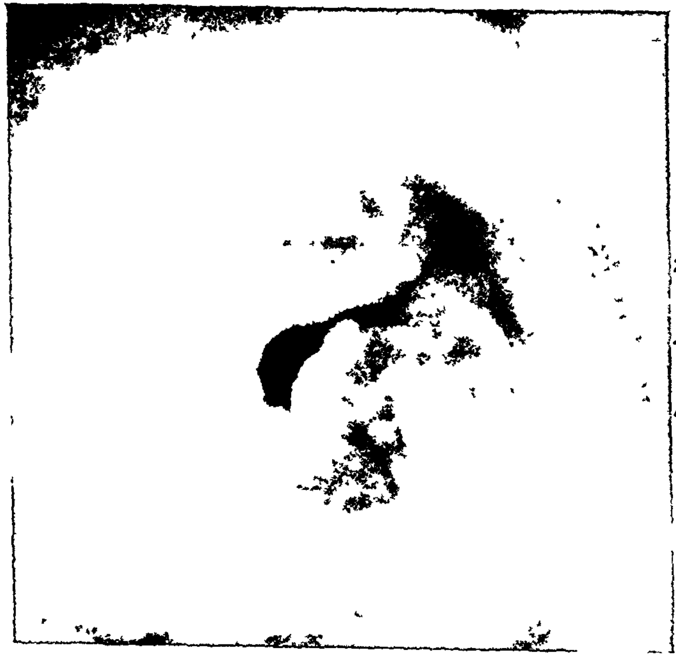


FIGURE 2A

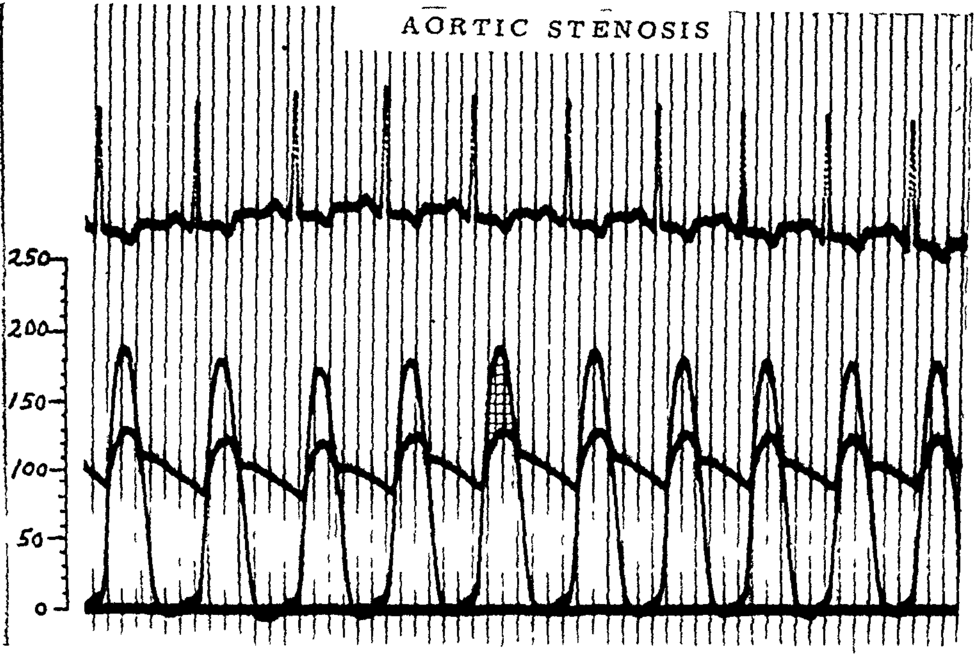


FIGURE 2B

Figure 2A: Cinematophotograph of a perfused aortic valve at height of systole in patient with aortic stenosis. Note fusion of leaflets and small orifice. Compare with Figure 1A.—*Figure 2B:* Left ventricular and aortic pressures in aortic stenosis. Shaded area represents systolic pressure gradient.

TABLE III
AORTIC STENOSIS (45 CASES)

Cardiac Size	
Normal	7
Borderline	6
Plus 1	17
Plus 2	13
Plus 3	2
Aortic Valve Calcification	41 (91 per cent)

normal in only two. One of these had a congenital lesion. In the remainder the second sound was either much diminished (17 cases) or absent (26 cases). On admission six patients (not included in the 11 mentioned at the end of the last paragraph) had signs of congestive heart failure, as evidenced by basal pulmonary rales and/or peripheral edema.

Left ventricular hypertrophy or strain was the most frequent finding in the electrocardiogram (33 cases). Left bundle branch block was seen in three. In four tracings the ST-T changes were thought due to digitalis therapy alone, while non-specific T wave abnormalities were observed in three instances. In one patient the electrocardiogram was suggestive of coronary artery disease.

The roentgenologic findings revealed a normal cardiac size in seven. There was a suggestion of left ventricular hypertrophy, in the form of rounding of the lower left cardiac border, but no over-all enlargement. Borderline enlargement was seen in six instances. The heart was moderately enlarged, 1-2 plus, in 20 cases and considerably enlarged, 3 plus, in only two. It should be noted that no Grade IV cardiac enlargement was seen.

Aortic calcification was observed roentgenographically in 29 patients, and found in an additional 12 at surgery. Planigrams were done in only a few cases, but probably would have increased the number of positive x-ray findings, if they had been done routinely.

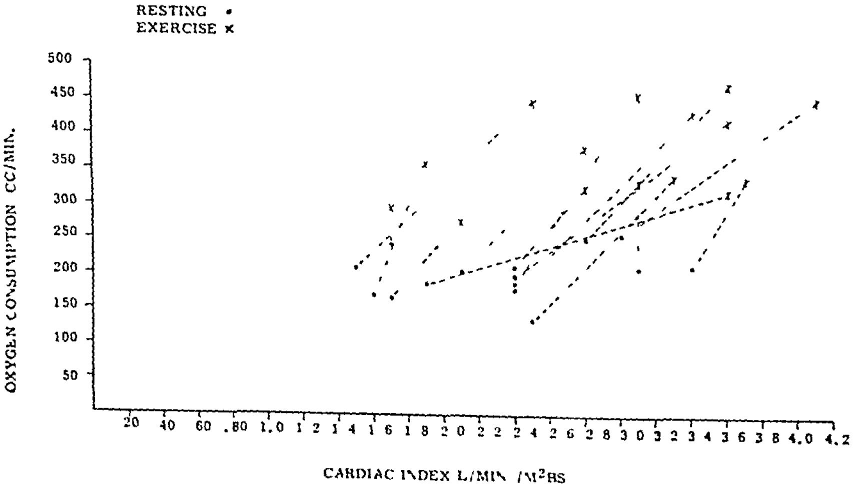


FIGURE 3: Effect of exercise upon the cardiac index in aortic stenosis.

Discussion

In any consideration of the physiologic data in aortic stenosis the most significant findings needing discussion are the low cardiac output and the pressure gradient across the valve.

The commonest cause of a decreased output in heart disease is cardiac failure, especially left ventricular failure. This cannot be excluded as a factor in any of our cases, especially where clinical failure had been present in the past. However, some patients with no history of failure had just as low an output. One could say that they were examples of subclinical failure, but it is also possible that the valvular obstruction *per se* may contribute to the low output.[12]

In order for the output to be maintained at normal levels, with a narrowed orifice, the ejecting force must increase. One might expect that this force could increase in proportion to continued narrowing at the valve. Actually, one finds that the systolic ejection pressure rarely rises above 250 to 300 mm. of Hg.[16]; presumably the myocardium is incapable of generating any higher pressure. If one wishes to define this as failure, then we find ourselves dealing in semantics. The fact is that this same myocardium, 10 days after the valve has been opened, has been shown in some cases capable of increasing the output.[17]

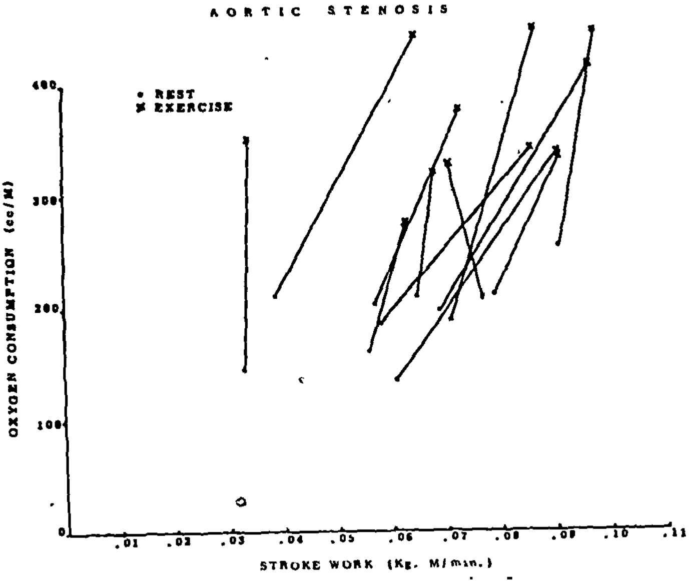
Even where the resting output is normal, there may be a failure to increase the output normally on exercise. Here again myocardial failure or valvular obstruction or both may play a role.

The rise in systolic pressure in the ventricle is the means by which this chamber maintains the cardiac output. It is this rise, coupled with the valvular obstruction which leads to the pressure gradient across the valve, which is so characteristic of dynamic aortic stenosis. The rise in pressure is responsible for the rise in total left ventricular work, since this factor is included in the formula for total work. A marked fall in the cardiac output could result in a lesser rise or even a fall in work, and it is certainly true that in severe heart failure, the total work will fail, as the left ventricle be comes incapable of producing a marked rise in systolic pressure.

The increase in work may be looked on as a cause of the resulting hypertrophy of the myocardium. This in turn may enable the ventricle to raise the systolic pressure still higher. However, the degree to which hypertrophy may go on is limited by the coronary blood flow. Certain it is that it does not go on ad infinitum. The aortic obstruction imposes some limits on the perfusion pressure available for the coronary vessels, and also on the output available for them. Moreover, the increased systolic resistance to flow in the hypertrophied muscle cuts down on whatever coronary flow

TABLE IV
AORTIC STENOSIS—ELECTROCARDIOGRAM FINDINGS (45 CASES)

Left Ventricular Hypertrophy and Stain	33
Left Bundle Branch Block	3
Digitalis Effects	4
Non-specific Changes	3
? Coronary Artery Disease	1



AORTIC STENOSIS (INCIDENCE OF SYMPTOMS)

FIGURE 4: Effect of exercise on the stroke work of the left ventricle in aortic stenosis.

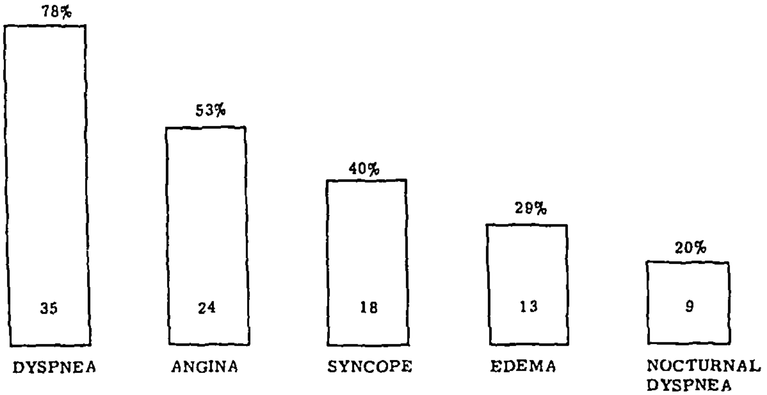


FIGURE 5: Incidence of symptoms.

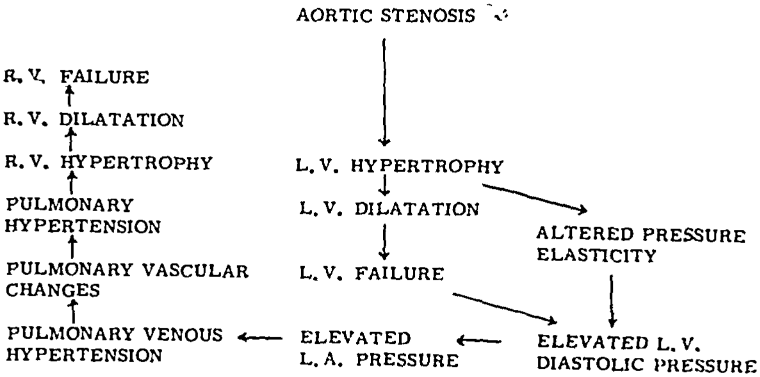


FIGURE 6: Patho-physiologic changes in the course of aortic stenotic valvular disease.

normally does occur in systole. For these reasons hypertrophy is not a process which can occur indefinitely.

It is doubtful if one should wish it to be so, since the thickened muscle does not have normal distensibility. As the pressure-volume relations of the myocardium alter as a result of the hypertrophy the end diastolic pressure in the ventricle rises.[7] The left atrial pressure likewise must rise to permit blood to flow into the less distensible ventricular chamber. This is most noticeable at the end of diastole, when a giant "a" wave is seen in the left atrial pressure tracing. A similar phenomenon has been observed in the right atrial pressure curve in cases of pulmonic stenosis or other cause of right ventricular hypertension.[13]

Any discussion of an elevated left atrial pressure leads backwards to a mention of pulmonary hypertension. Certainly this is a cause of elevated pulmonary vascular pressure and resistance. Such an elevation, whether acute as in sudden left ventricular failure, or chronic due to the diminished distensibility of the left ventricular myocardium, may result in anatomic pulmonary vascular changes.[14] These in turn elevate the pulmonary artery pressure still further as long as the right ventricle maintains its output. Later, when the right ventricle can no longer maintain this output, failure of this chamber occurs and is manifested by hepatomegaly and peripheral edema.

The diagram shown in Figure 6 summarizes these patho-physiologic changes in the course of stenotic aortic valvular disease.

The three chief clinical manifestations of the disease also merit brief comment.

Dyspnea, primarily exertional, is the commonest symptom. Is this truly due to left ventricle failure? If one considers failure the inability of the heart to meet the demand of the tissues, then this must be considered to be failure. However, as pointed out above, we believe it possible for the left ventricular diastolic pressure, the atrial pressure and the pulmonary venous pressure to rise, early in the course of the disease, simply because of the hypertrophy of the left ventricle. When this occurs, pulmonary congestion and exertional dyspnea may ensue, even though the myocardium has not truly failed, except in the face of the stenotic valve. At this stage surgical opening of the valve would probably give the most satisfactory results (assuming that calcification was not so massive as to prevent adequate mobility), since the myocardium would still be in reasonably good condition. Perhaps, even earlier surgical intervention, in the absence of symptoms, before much hypertrophy has occurred, would be preferable, when the mortality of surgery is sufficiently low to warrant intervention at this stage of the disease.

Angina in these patients represents a disproportion between the coronary blood flow and the demands of the hypertrophied myocardium. Atherosclerosis probably plays only a small part in the production of this symptom, although if present to any degree would undoubtedly aggravate the coronary insufficiency. The hypertrophied muscle mass has probably outgrown its coronary vasculature. The work of the left ventricle has doubled or tripled while cardiac output may be normal or low; hence the coronary flow is likewise normal or below. Herein lies the major reason for the disproportion. A minor additive factor is probably the increased systolic resistance to flow in the muscle itself, decreasing whatever systolic flow does occur in the myocardium.

Syncope has been explained by Marvin and Sullivan[15] as due to a hyperactive carotid sinus. However, the disappearance of this symptom after cardiac surgery makes this explanation unlikely.[17] It seems more likely that an inadequate cerebral blood flow secondary to an inadequate rise in cardiac output with exercise is the major cause of effort syncope in aortic stenosis. Such cerebral blood flow measurements in patients with this disease under conditions of rest and exercise, have not been made, but would be worth doing in the investigation of this problem. The findings after exercise, when the cardiac output is measured, certainly point in this direction.

Finally, some reasons for our failure to correlate symptoms with the pathologic physiology should be offered. We had expected that perhaps the degree of dyspnea would correlate with the left ventricular diastolic pressure, or the pulmonary artery pressure or perhaps inversely with the cardiac output; or that angina would be related to left ventricular work, or aortic valve flow or a combination thereof; or that the severity of syncopal attacks might show a relation to the cardiac output or the aortic valve area. Why were these expectations not fulfilled?

First, the symptomatology was graded on the basis of the patient's subjective description of a period in his life covering perhaps six months or longer prior to admission, while the physiologic data were obtained at a relatively instantaneous moment in his hospitalization. Second, the symptoms described the individual's response to various activities, while the catheterization data were obtained at rest in the majority and in a small number of cases during exercise, but the relationship of this exercise to daily activity is not known. Third, the actual grading of symptoms is probably subject to serious error, since individuals may make different demands on their hearts even where the pathology is similar. The attempt to grade the symptoms or the physiologic data produced several groups with small numbers of patients. Finally, we must admit that the physiologic data fail to evaluate the myocardial factor, which may be as important as the valvular obstruction in the production of the pressure gradient and hence greatly influence the magnitude of the cardiac output.

Conclusions

It would appear that once a patient with aortic stenosis develops dyspnea, angina or syncope, or some combination of these, a physiologically significant degree of obstruction is present and the aortic valve area is less than 1 cm.^{2} one-third of normal. That a critical aortic valve area exists was suggested by others.[16] Once the valve orifice has been reduced to this critical size, then the type and degree of symptoms may be variable. Electrocardiographic and x-ray evidence of left ventricular enlargement only confirm the physiologic significance of the lesion. This concept is confirmed also by the physiologic and clinical changes that follow surgery for this lesion. After aortic commissurotomy, Smith and associates[17] found in 17 patients in this series that although the pressure gradient is only occasionally eliminated (in two cases) and physiologic obstruction is still present, the symptom triad of dyspnea, angina and syncope is relieved in those cases where the calculated post-operative valve area has been brought above 1 cm.^{2}

SUMMARY

1. The physiologic and clinical characteristics of aortic stenosis are presented in 45 cases studied by combined heart catheterization, 39 of which came to surgery.

2. A constant finding is the presence of a systolic pressure gradient at the aortic valve. The aortic valve flow is generally reduced, and the average valve area was calculated to be 0.5 cm.^{2} (normal 3.0 cm.^{2}).

3. The clinical triad of dyspnea, angina and syncope or some combination of these appear when the valve area is reduced below 1.0 cm.^{2} The lack of correlation between the physiologic data and the severity of symptoms is discussed.

Acknowledgments: The authors wish to express their appreciation to Mr. George Raber and the Misses Betty Underwood, Ruth Freeman and Evelyn DeSimone for their technical assistance, and to the other members of the catheterization team.

RESUMEN

1. Se describen la fisiología y las características clínicas de la estenosis aórtica en 45 casos estudiados por la combinación de la cateterización cardiaca. De ellos, 39 se sujetaron a la cirugía.

2. Un hallazgo constante es la presencia de un gradiente a la presión sistólica en la válvula aórtica. El flujo de la válvula es generalmente reducido y el término medio de área de la válvula se calcula de 0.5 cm. 2 (normal: 3.0 cms. 2).

3. La triada clínica de disnea, angina y síncope o alguna combinación de estos, aparece cuando la válvula se reduce hasta abajo de 1.0 cm. 2. La falta de correlación entre los datos fisiológicos y la gravedad de los síntomas es motivo de consideraciones.

RESUME

1. Les auteurs rapportent, les caractéristiques physiologiques et cliniques de la sténose aortique dans 45 cas, étudiés avec cathétérisme cardiaque. Parmi eux, 39 furent opérés.

2. Une constatation constante est donnée par le gradient de la pression systolique au niveau de la valvule aortique. Le débit de cette valvule aortique est généralement réduit, la surface valvulaire moyenne représentait selon leurs calculs 0,5 cm2 alors que la normale est de 3 cm2.

3. La triade clinique dyspnée, douleur constrictive et syncope, ou une combinaison quelconque de ces symptômes, apparait lorsque la surface valvulaire s'abaisse au-dessous de 1 cm2. Les auteurs discutent l'absence

de corrélation entre les données physiologiques et la sévérité des symptômes.

ZUSAMMENFASSUNG

1. Es werden die physiologischen und klinischen Merkmale der Aortenstenose dargestellt an 45 mit kombinierter Herz-Katheterisierung untersuchten Fällen, von denen 39 zur Operation kamen.

2. Ein gleichbleibender Befund ist das Bestehen eines systolischen Druckgefälles an der Aortenklappe. Die Durchströmung an der Aortenklappe ist für gewöhnlich verringert, und der durchschnittliche Klappenbereich wurde mit 0,5 qcm errechnet (normal = 3,0 qcm).

3. Die klinische Trias von Kurzatmigkeit, Angina und Kollaps oder irgendeine Kombination dieser Symptome tritt auf, sobald das Klappenareal unter 1,0 qcm verringert ist. Besprechung des Fehlens der Korrelation zwischen den physiologischen Daten und der Schwere der Symptome.

REFERENCES

1 Likoff, W. and Bailey, C. P.: "Surgical Management of Aortic Stenosis; an Evaluation of Techniques and Results," *Arch. Int. Med.*, 99:859, 1957.
2 Levine, S. A.: *Clinical Heart Disease*, 4th Ed. Philadelphia, 1951, W. B. Saunders Co.
3 White, P. D.: *Heart Disease*, New York, 1951, MacMillan Co.
4 Mitchell, A. M., Sackett, C. H., Hunzicker, W. J. and Levine, S. A.: "The Clinical Features of Aortic Stenosis," *Am. Heart J.*, 48:684, 1954.
5 Bougas, J., Musser, B. G. and Goldberg, H.: "Left Heart Catheterization; I Clinical Methods and Applications," *Am. Heart J.*, 52:359, 1956.
6 Musser, B. G., Bougas, J. and Goldberg, H.: "Left Heart Catheterization; II With Particular Reference to Mitral and Aortic Valvular Disease," *Am. Heart J.*, 52: 567, 1956.
7 Goldberg, H., Dickens, J., Raber, G. and Hayes, E.: "Simultaneous (Combined) Catheterization of the Left and Right Heart," *Am. Heart J.*, 53:579, 1957.
8 Froher, D. L.: "Use of Pressure Recordings Obtained at Transthoracic Left Heart Catheterization in the Diagnosis of Valvular Heart Disease," *J. Thoracic Surg.*, 30:379, 1955.
9 Bjork, V. D., Malstrom, G. and Uggla, L. G.: "Left Auricular Pressure Measurement in Man," *Ann. Surg.*, 138:718, 1953.
10 Moscovity, H. L., Gordon, A. J., Braunwald, E., Amram, S. S., Sapin, S. D., Lasser, R. D., Himmelstein, S. and Ravitch, M. D.: "The Use of Simultaneous Left Pressure Pulse Measurements in Evaluating the Effects of Mitral Valve Surgery," *Am. J. Med.*, 18:406, 1955.
11 Gorlin, R. and Gorlin, S. G.: "Hydraulic Formulae for Calculation of Stenotic Mitral Valve and other Valves and Central Circulatory Shunts," *Am. Heart J.*, 41:1, 1951.
12 Goldberg, H., Bakst, A. A. and Bailey, C. P.: "Dynamics of Aortic Valvular Disease," *Am. Heart J.*, 47:527, 1954.
13 McCord, M. D., Komess, S. and Blount, S. G., Jr.: "The Characteristics of the Right Atrial Pressure Wave Associated with Right Ventricular Hypertrophy," *Am. Heart J.*, 45:706, 1953.
14 Smith, R. C., Burchell, H. B. and Edwards, J. E.: "Pathology of the Pulmonary Vascular Tree IV. Structural Changes in the Pulmonary Vessels in Chronic Left Ventricular Failure," *Circulation*, 10:801, 1954.
15 Marvin, H. M. and Sullivan, A. G.: "Clinical Observations Upon Syncope and Sudden Death in Relation to Aortic Stenosis," *Am. Heart J.*, 10:705, 1935.
16 Gorlin, R., MacMillan, I. K. R., Medd, W. E., Mathews, M. B. and Daley, B.: "Dynamics of the Circulation in Aortic Valvular Disease," *Am. J. Med.*, 18:855, 1955.
17 Smith, R. C., Bailey, C. P. and Goldberg, H.: "Aortic Commissurotomy: A Physiologic Evaluation by Combined Heart Catheterization," *J. Thoracic Surg.*, In press.

The Normal Phonocardiogram of the Aged*

C. ARAVANIS, M.D.**
Chicago, Illinois
and
R. HARRIS, M.D.†
Albany, New York

The gradually increasing interest in exact knowledge of the data concerning the *senile heart* indicated the need for an exact study of phonocardiography which would indicate the limits within which the heart sounds could be considered normal. Similar studies have been made in the heart of the normal adult (Rappaport and Sprague,[1] Luisada et al.[2]) and in that of the normal child (Aravanis and Cardi[3]). Collateral data dealing with the electrocardiogram, the pulse rate, the heart x-ray films and the blood pressure have been collected in order to prove that the cardiovascular system of the patients was not affected by disease.

Material and Method

In order to evaluate the heart sounds of elderly persons with clinically normal hearts, a phonocardiographic investigation was performed in 100 people between the ages of 60 and 108. The majority of them were selected from a group of 600 permanent residents at the Ann Lee Home. A few were obtained from the Troy Jewish Home for Aged and the Albany Home for Aged of the Little Sisters of the Poor. Sixty-nine were men; 31 were women. Table I shows the age distribution of the patients. The final selection was made on the basis of normal history and physical examination, normal blood pressure, normal cardiac silhouette in the roentgenogram, and the absence of definite ECG changes. Persons with a history of dyspnea, angina, coronary occlusion, or heart failure, or receiving cardiac drugs, were excluded. Thus, the possibility of significant heart disease which could influence or change the heart sounds was greatly eliminated. Most of these residents were in the Home only because of their age. A few had senile disorders which did not affect the heart.

"Stethoscopic" and "logarithmic" phonocardiograms were taken over the routine five precordial areas as described elsewhere[7] with a Sanborn Twin-Beam Cardiette. Simultaneous carotid pulse tracings were also recorded.

Analysis of Data

Phonocardiogram—Heart Sounds. The duration of the first and second heart sounds was measured in the "stethoscopic" tracing. The first sound was measured at the apex; the second, at the base. Two measurements

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*From the Division of Cardiology, The Chicago Medical School and the Ann Lee Home, Albany, New York. This study was aided by a grant of the Albany Heart Association.

**Research Associate, Division of Cardiology, The Chicago Medical School.

†Attending Cardiologist, St. Peter's Hospital, Albany, New York.

TABLE I
AGE DISTRIBUTION

60 - 69	27 Cases
70 - 79	28 Cases
80 - 89	31 Cases
90 - 108	14 Cases

TABLE II
DURATION OF HEART SOUNDS

Age	First Sound		Second Sound	
60 - 69	Total duration	0.182	Total duration	0.110
	Central phase	0.052	Central phase	0.042
70 - 79	Total duration	0.174	Total duration	0.109
	Central phase	0.051	Central phase	0.044
80 - 89	Total duration	0.168	Total duration	0.102
	Central phase	0.055	Central phase	0.039
90 - 108	Total duration	0.158	Total duration	0.094
	Central phase	0.054	Central phase	0.039

TABLE III
DISTANCE BETWEEN FIRST AND SECOND SOUND

Age	Seconds	
60 - 69	0.333	
70 - 79	0.330	With a mean value
80 - 89	0.325	for all ages 0.336
90 - 108	0.320	

TABLE IV
BLOOD PRESSURE ACCORDING TO THE AGE GROUP

60 - 69	Men	137/84	138/83
	Women	139/79	
70 - 79	Men	132/83	135/85
	Women	136/84	
80 - 89	Men	131/85	133/83
	Women	135/81	
90 - 108	Men	131/70	130/77
	Women	137/88	

Average pulse rate for all ages = 81 per minute.
Average QT Ratio = 1.02 for all ages.

were done: *the total duration* of each sound from the beginning to the end, and the duration of their *central phase.* This last measurement excludes several low-pitched vibrations both at the beginning and at the end of each sound.

The *average total durations of both sounds* were found to be prolonged, but not significantly so (Table II). As the age increases, the *average total duration* of *the first sound* progressively diminishes from 0.182 second, in the group 60-70, to 0.158 second, in the group 90-108. On the contrary, the *average duration of the central phase of the first sound* does not change significantly, although it shows a slight increase (from 0.052 for the ages 60-70 to 0.054 for the ages 90-108). The *average total duration of the second sound* also decreases with age (0.11 in the age group 60-69, 0.094 in that 90-108). The *average duration of the central phase of the second sound* decreases from 0.042 in the age group 60-70 to 0.039 in the age group 90-108.

The distance between the first and second sound (*mechanical systole*) was found slightly decreasing as the age increases, with an average value of 0.325 second (Table III).

A *fourth heart sound* of normal amplitude was found in 21 cases (21 per cent); in two of them, the amplitude of this sound was high but the pitch was low, so that it did not fulfill the criteria of a presystolic gallop.

A large low-pitched vibration at the end of the first sound was found in a high percentage of this group. There is the opinion that this is a *vascular* vibration (aortic or pulmonic).

A *third heart sound* of small amplitude was present in two cases (2 per cent).

Murmurs. No significant murmur was found in the group. This was expected on the basis of the criteria for selection. In 13 cases (13 per cent), a small systolic murmur was recorded over both the apex and the base of the heart. This was a decrescendo murmur with a regular type of vibration (musical murmur). A_2 and P_2 were normal.

ECG. None of the patients had an abnormal ECG as a result of the selection. In three, occasional auricular extrasystoles were present, and in two the P-R interval was 0.22 of a second (this may still be considered within the upper limits of normal).

Blood pressure. The average figures according to age and sex are shown in Table IV. It is apparent that both the systolic and the diastolic pressures *decrease* as the age increases, both in men and women. This fact is more pronounced among men. It should be remembered that hypertensive patients were not considered.

X-Ray Films. In all cases, a chest x-ray film was taken in the P-A position and in deep inspiration. It was found that, in 29 cases (29 per cent), the heart was slightly increased in size, usually because of left ventricular enlargement. However, some of the films reveal that the patient was not in deep inspiration during the exposure. Therefore, the findings are not absolutely comparable. The aorta was found to be wide and tortuous in

74 per cent of the cases. Forty-four per cent had calcifications in the aortic arch. Only 23 per cent had a normal aorta.

Q-T Ratio. The Q-T ratio was measured in order to see whether old people have the same values as younger persons. The average QTr for all ages was found to be 1.02. The lowest value was 0.80, and only one case had a value of 1.20.

Pulse Rate. The average pulse rate for all ages and for both sexes was 81 per minute. No significant difference was found between the different ages and between men and women.

Pulse Tracing. The carotid tracing was taken by using a small funnel, which was held by the hand against the right carotid artery. A normal pulse tracing was found in all cases. A rapid rise, a rather slow fall, and a marked dicrotic wave were typical. The distance between the largest vibration of the first sound and the end of the ascending limb of the pulse was from 0.06 to 0.08 second. This confirms our findings in a previous study in cases with relative and organic aortic stenosis.[4] In relative stenosis, the distance between first sound and ascending limb of the pulse was about the same as that found here; in organic stenosis, it was prolonged. The peak of the pulse was rounded in 63 per cent of the cases, a fact which was considered evidence of arteriosclerosis of the aorta. An anacrotic notch was not present but, in 13 cases, a shallow depression existed in the ascending branch and was considered equivalent to this notch. The catacrotic notch was present in all cases and coincided with the second aortic sound.

Blood Count. A normal red blood count was found in all cases, although a tendency to higher values was encountered in a good percentage of them. Forty per cent of the cases had more than five million red cells, with a normal amount of hemoglobin. This is probably the result of chronic pulmonary emphysema.

Discussion

This study was made in 100 selected senile persons between the ages of 60 and 108. As a condition for the selection of the cases was the absence of high blood pressure, and the absence of any relevant change of the electrocardiogram, it is self-understood that these abnormalities were absent.

The duration of the heart sounds was measured in the phonocardiogram. The *average total duration of the first sound* was found only slightly prolonged in comparison with the normal adults.[1] As the age increased, the total duration of the sounds decreased. On the other hand, the duration of the central phase of the sound did not change with increased senility.

The *average total duration of the second sound* also decreased with age but, in contrast with the first, the duration of the central phase also decreased. The importance of this phase is that it is made of large, high-pitched vibrations and is the only part which is clearly audible. Therefore, one would expect shorter, more snapping heart sounds upon auscultation of subjects of advanced age.

Collateral data of interest were:

(a) A slight tendency to a decrease of blood pressure with age.
(b) A normal pulse rate.
(c) A normal QT ratio in the electrocardiogram.
(d) An average duration of mechanical systole of 0.336.
(e) A trend toward a slight increase of red blood cells with age.
(f) A rapid rise, a slow fall, and a high dicrotic wave in the pulse.
(g) A slight enlargement of the left ventricle revealed by chest films.

SUMMARY

A phonocardiographic study was made in 100 old persons selected because of the absence of data indicating heart disease.

The heart sounds were found to slightly decrease in duration with advanced age.

Collateral data which were collected were: pulse rate, duration of ventricular systole, QT ratio, hematological, roentgenological and sphygmographic data.

The above tabulated phonocardiographic data can be used for comparison in the study of tracings of old patients presenting murmurs or other auscultatory abnormalities.

We wish to thank Mrs. P. Hinds and Mrs. Harris for their technical assistance.

RESUMEN

Se hizo un estudio fonocardiográfico en 100 ancianos escogidos por su ausencia de datos indicadores de enfermedad cardiaca.

Los ruidos cardiacos se encontraron ligeramente disminuídos en su duración en la edad avanzada.

Los datos colaterales que se obtuvieron fueron: frecuencia de pulso, duración de sístole ventricular, relación QT, hematología y datos esfigmográficos.

Los datos fonocardiográficos arriba tabulados pueden ser usa dos para comparar en el estudio de los trazos de las personas ancianas presentando soplos u otras anormalidades auscultatorias.

RESUME

Une étude phonocardiographique fut pratiquée chez 100 personnes âgées choisies à cause de l'absence d'éléments indiquant chez elles l'existence d'une affection cardiaque.

D'après ces observations, les bruits du coeur semblent diminuer légèrement en durée avec l'âge.

Parallèlement furent recueillis des éléments concernant la fréquence du pouls, la durée de la systole ventriculaire, l'état du tracé QT, des constatations hématologiques, radiologiques et sphygmographiques.

Les données phonocardiographiques ci-dessus rassemblées peuvent être

utilisées pour l'étude des tracés des malades âgés présentant des souffles ou d'autres anomalies d'auscultation.

ZUSAMMENFASSUNG

Eine phonocardiographische Untersuchung wurde angestellt bei 100 alten Menschen, deren Auswahl erfolgte wegen des Fehlens von Angaben, die auf eine Herzerkrankung hinwiesen.

Es fand sich, dass die Herztöne etwas an Dauer abnahmen mit zunehmenden Alter.

Gleichlaufende Werte, die erhoben wurden, bestanden in: Pulszahl, Dauer der ventrikulären Systole, QT—Verhältnis, haematologische, röntgenologische und spyhgmographische Werte.

Die wie oben tabellenförmig zusammengefassten phonocardiographischen Daten lassen sich zum Vergleich verwenden bei der Untersuchung von Kurven alter Menschen, die Geräusche oder andere auskultatorische Abweichungen bieten.

REFERENCES

1 Rappaport, M. B. and Sprague, H. B.: "The Graphic Registration of the Normal Heart Sounds," *Am. Heart J.*, 23:591, 1942.

2 Luisada, A. A., Mendoza, F. and Alimurung, M. M.: "The Duration of the Normal Heart Sounds," *Brit. Heart J.*, 11:41, 1949.

3 Aravanis, C. and Cardi, L.: "Physiological Range of Electrical Systole and Heart Sounds in Children," *Cardiologia*, 28:269, 1956.

4 Aravanis, C. and Luisada, A. A.: "The Murmur in Aortic Stenosis," *Am. Heart J.* (in press).

5 Luisada, A. A.: *The Heart Beat*, Paul B. Hoeber, New York, 1953.

CURRENT THERAPY

The Editorial Board invites your comment.

The Lipid Problem in Atherosclerosis

WELDON J. WALKER, COLONEL, MC*
Fort Sam Houston, Texas

Atherosclerosis is a disease process involving primarily the intima of the main coronary arteries, the aorta and the major arteries of the cerebrum and lower extremities. The lesions tend to be patchy and plaque-like. Symptoms are produced by occlusion of the lumen of the vessel with impairment of blood flow to the organ involved. This is usually accomplished by a progressive increase in the size of the atheromatous plaque or by the formation of a thrombus on the plaque. Occasionally the atheromatous process extends into the media with weakening of the vessel wall with aneurysm formation. Benign Monkeberg's mediocalcinosis or the diffuse arteriosclerosis encountered in severe hypertension is not being considered.

Undoubtedly many factors are important in the genesis of atherosclerosis. However, there is abundant evidence that elevated levels of serum cholesterol, various classes of B-lipoproteins, and probably other lipid factors such as fatty acids and triglycerides are of paramount importance in the development of atherosclerosis and its complications. Because of the conflicting data and the numerous gaps in our knowledge concerning the metabolism of cholesterol and other lipids, many have felt that the clinician should avoid attempts to draw therapeutic implications at the present state of our knowledge. However, since more Americans die from coronary atherosclerosis alone than from all forms of malignancy combined,[1] it would seem imperative to ask if the practicing physician is not justified in drawing a few tentative conclusions from the mass of conflicting and inadequate data so long as these therapeutic views and conclusions are not potentially harmful to the patient and remain flexible enough to be modified as additional facts become available.

The principle evidence linking atherosclerosis with altered cholesterol metabolism is as follows: Experimental lesions can be produced in numerous laboratory animals by feeding cholesterol and by other dietary procedures. The experimental lesions are always preceded by an elevation of serum cholesterol. The lesions themselves have a high cholesterol content. If the animal's diet is altered so that serum cholesterol is reduced, the experimental lesions tend to regress. An increased incidence of atherosclerosis is observed in clinical states associated with hypercholesteremia such as xanthoma tuberosum, myxedema, diabetes and nephrosis. Individuals who suffer myocardial infarctions early in life tend to have higher levels of serum cholesterol and lipoproteins than the general population. However, there is no direct evidence that dietary cholesterol elevates serum lipid levels or causes atherosclerosis in humans. This is probably due to the fact that total circulating cholesterol in humans is largely endogenous in origin.[2] There is accumulating evidence that elevated serum lipid levels, in addition to their importance, in the development of atheromatous lesions, may also be involved in the development of the major complication of atherosclerosis, namely thrombus formation. Several studies have indicated an increased clotting tendency in the presence of elevated serum lipids.[3, 4]

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*Chief of the Cardiovascular Service, Brooke Army Hospital. Presently stationed at the 97th General Hospital, A.P.O. 757, New York, New York.

Factors Known to Lower or Alter Serum Lipids in the Human

Nutrition and Diet

Knowledge is now available that enables one to understand and reconcile many of the conflicting claims of the past. Insurance studies have long indicated an increased death rate from diseases due to atherosclerosis in overweight individuals and a low death-rate from these diseases in lean individuals. Furthermore, it has been demonstrated that obese individuals who reduce their weight also reduce their expected mortality from these diseases.[5] Clinical studies have revealed significantly higher average levels of serum cholesterol and certain lipoproteins in overweight persons.[6] Weight reduction has been shown to lower these levels and positive caloric balance to elevate them even on a fat free, cholesterol free diet.[7] (A diet that causes the body to form fat containing highly saturated fatty acids). Increased caloric intake was not associated with elevated serum lipids if there was an equal increase in physical activity.[8] Others have emphasized the correlation between high dietary fat intake, elevated levels of serum cholesterol, and a high incidence of atherosclerosis.[9] The decreased death rate from atherosclerosis in various occupied countries during World War II, has also been attributed to the low dietary fat intake at that time. Since overweight individuals tend to ingest more calories and fat than lean individuals, it has been difficult to decide whether the state of nutrition or the increased dietary fat was the essential factor in the observed increased incidence of atherosclerosis and elevated lipid levels. A recent study in which a group of patients with atherosclerosis sustained a large weight loss while ingesting a diet extremely high in animal fat indicated that the S_f 0-12 classes of B-lipoproteins are directly influenced by dietary fat intake, while the S_f 20-400 fraction appears to be more directly influenced by the state of nutrition.[10] This, (along with other data) suggests that both obesity and dietary fat intake may be independent predisposing factors in the development of atherosclerosis. Evidence is accumulating that the type of fat ingested may be much more important than the mere quantity consumed. The ingestion of fats composed largely of saturated fatty acids such as occur in most animal fats or vegetable fats that have been hydrogenated and converted to a solid state tend to elevate serum cholesterol and lipoprotein levels while large amounts of unsaturated essential fatty acids, such as linoleic acid, which cannot be synthesized in the body, tend to lower serum cholesterol levels.[11] The essential fatty acids are thought to be important in the transport of cholesterol.[12] Of the available vegetable oils, safflower oil and corn oil, have the highest content of linoleic acid.

Female Sex Hormone

Premenopausal women are relatively "immune" to the complications of atherosclerosis. In addition, they have lower levels of serum cholesterol and B-lipoproteins than males of comparable age and state of nutrition. Following the menopause, or after surgical castration, the female loses her protection against atherosclerosis and manifests significantly higher serum lipid levels.[6, 13, 14] The administration of estrogens to males or to postmenopausal women causes an alteration of the serum lipid pattern toward that of the premenopausal woman.[15]

Heparin

Intravenous heparin has been demonstrated to accelerate the clearing of neutral fat which produces turbidity of the serum in the post-absorptive state. Heparin appears to produce this effect by activating a tissue enzyme lipoprotein lipase. The role of heparin and this enzyme in the intermediary metabolism of cholesterol is not clear.

Other Agents

Nicotinic acid when administered in extremely large doses has been reported to lower serum cholesterol levels.[16] If further reports confirm this effect, the unpleasant side effects from the large dose required will still limit its clinical usefulness. Plant sterols such as B-sitosterol have been reported to lower serum cholesterol by interfering with its absorption from the gut. Since dietary or exogenous cholesterol appears to be relatively unimportant in human atherosclerosis one is not surprised by the divergent reports that have appeared in the literature concerning its effects.

Therapeutic Application

If the physician is to employ any of the dietary measures or therapeutic agents thought to alter serum lipids, how is he to select the patients to be treated? Since many patients manifest no clinical evidence of atherosclerosis prior to the moment they are stricken by a fatal "coronary," one would not wish to wait until then. The U. S. Public Health Service has recently completed an extensive study concerning the relative predictive value of serum cholesterol and lipoprotein levels in determining those patients who will later manifest overt atherosclerosis.[17] While most patients who developed coronary atherosclerosis during the study were those with high cholesterol and lipoprotein levels, a significant number occurred in those with low levels. It was concluded that neither determination was of much value in predicting clinical atherosclerosis in the individual case. In general the more economical serum cholesterol determination had the greater value. Since there is a tendency for serum cholesterol levels to fluctuate widely from time to time in any individual, the average of several determinations would probably have greater predictive value than a single determination. However, it is doubtful that any determination will ever have significant individual predictive value since latent atherosclerosis without clinical manifestations occurs almost universally among adult American males.[18] In fact lipid deposits start forming in the arterial walls during childhood.[19] Consequently, all adult males and post-menopausal females are candidates for the complications of atherosclerosis since most already have the disease, (i. e., individuals vary chiefly in the degree of involvement and the location of their lesions). The patient who dies of a fatal coronary occlusion may have only one-tenth the total atherosclerosis of his neighbor, whose larger and more extensive lesions are primarily in the aorta, do not interfere with blood flow, and produce no symptoms. Since most atheromatous lesions probably develop over a period of many years and there is no adequate way of predicting when the complication of thrombosis will occur, it would seem wise to institute prophylactic measures that may impede the development of atherosclerosis before it is far advanced. Since the disease process is practically universal and there is no satisfactory test to predict who will be stricken, a tentative interim preventive program is proposed for all adult males and post-menopausal females. The program should be modified as new knowledge becomes available. This program can be followed with varying degrees of flexibility. Relatively rigid adherence is proposed for those individuals with overt atherosclerosis, those with a strong familial history of the disease or those with known hypercholesteremia or hyperlipemia. It is possible to follow this program and still enjoy palatable and satisfying meals. There is no evidence that any of the recommendations will be harmful to any patient, nor do they require serious alteration of his way of life. There is presumptive evidence that such a program will decrease the morbidity and mortality from atherosclerosis in the United States.

Proposed Program

1. Maintain weight at a lean level. Insurance statistics indicate that individuals approximately 10 per cent below "Ideal Weight," have greatest longevity;[20] they also have lowest serum lipid levels.[6] A liberal protein intake is recommended. Daily physical activity is probably desirable.[21]

2. The intake of animal fat and hydrogenated vegetable fats should be kept to a minimum. Fat should be trimmed from meats which should be cooked by broiling, boiling or stewing. Gravies are not recommended. Deep frying even with unsaturated vegetable oils rapidly lowers the iodine number of these oils. The ingestion of fried foods is not encouraged, e. g., boiled or poached eggs are more desirable than when fried or scrambled. Skim milk or buttermilk has most of the vitamins and minerals of whole milk without the animal fat and contains less than half the calories. Corn oil (much cheaper than safflower oil) can be used in the preparation of salad dressing or mayonnaise; with a bit of salt it is a satisfactory

substitute for butter on toast or bread. Most processed cheeses have a high fat content, cottage cheese is an excellent source of protein and is low in fat. Most pastries have a high fat content; angel food cake is an exception which is also a good source of protein. Fruits are excellent forms of fat free desserts. Patients with peptic ulcer will do just as well on a high-protein Sippy mixture made from skim milk, skim milk powder, egg white and flavoring, as on the conventional high fat program. The amphoteric action of proteins make them especially effective in neutralizing gastric acidity.

Specific Measures for Individual Patients

1. Estrogens: Castrate, hysterectomized females should probably receive estrogens at any age. Uterine bleeding is no problem, the increased risk of developing carcinoma is very slight and is far outweighed by the risk of early atherosclerosis. The same is true for the postmenopausal woman who has had her uterus removed. The dose of estrogen required to alter serum lipid levels will usually induce uterine bleeding in the non-hysterectomized postmenopausal woman. The decision to use it in such patients with atherosclerosis must depend on assessing all factors involved. The use of estrogens to decrease serum lipid levels in males with atherosclerosis will be influenced by assessing individual reactions to the feminizing side effects.

2. The use of intermittent heparin to alter serum lipid levels is still considered an experimental procedure. The use of Dicumarol or similar agents for long range anticoagulant effect appears promising for individuals who have sustained myocardial infarction but does not fall within the realm of this discussion.

REFERENCES

1 Prevention of Heart Disease: A Summary. The American Heart, Am. Heart Assn. New York, N. Y., April-June, 1951, p. 4.

2 Gould, R. G.: "Lipid Metabolism and Atherosclerosis," *Am. J. Med.*, 11:209, 1951.

3 Buzina, R. and Keys, A.: "Blood Coagulation After a Fat Meal," *Circulation*, 14: 854, 1956.

4 Sohar, E., Rosenthal, M. C. and Aldersberg, D.: "Plasma Lipids and Coagulation of Blood. Program Abstract, American Society for the Study of Arteriosclerosis," Chicago, Ill., Nov. 11-12, 1956. *Published in Circulation*, 14:479, 1956.

5 Dublin, L. I. and Marks, H. H.: "Mortality Among Insured Overweights in Recent years." *Read at the Sixtieth Annual Meeting of the Association of Life Insurance Medical Directors of America*, October 11-12, 1951.

6 Love, D. E. and Walker, W. J.: Relationship of Adiposity to Serum Cholesterol and Lipoprotein Levels. Summarized in Walker, W. J.: "Relationship of Adiposity to Serum Cholesterol and Lipoprotein Levels and Their Modification by Dietary means," *Ann. Int. Med.*, 39:705, 1953.

7 Walker, W. J., Lawry, E. Y., Love, D. E., Mann, G. V., Levine, S. A. and Stare, F. J.: "Effect of Weight Reduction and Caloric Balance on Serum Lipoprotein and Cholesterol Levels," *Am. J. Med.*, 14:654, 1953.

8 Mann, G. V.: *Serum Lipids during Positive Caloric Balance*, presented at the American Institute of Nutrition, San Francisco, Calif. Reported in *Pfizer Spectrum* July 9, 1955, J.A.M.A. p. 25.

9 Keys, A.: *Mode of Life and the Prevalance of Coronary Heart Disease.* Read at a Symposium on Arteriosclerosis at the University of Minnesota, *Minneapolis, Sept.* 7-9, 1955.

10 Walker, W. J., Weiner, N. and Milch, L. J.: "Differential Effect of Dietary Fat and Weight Reduction on Serum Levels of Beta-Lipoproteins," *Circulation*, 15:31, 1957.

11 Ahrens, E. H., Blankenhorn, D. H. and Tsaltas, T. T.: "Effect on Human Serum Lipids of Substituting Plants for Animal Fat in Diet," *Proc. Soc. Exper. Biol. and Med.*, 86:872, 1954.

12 Griffith, W. H.: "Fats in the Diet. Report to the Council," *J.A.M.A.*, 164:411, 1957.

13 Wuest, J. H., Dry, T. J. and Edwards, J. E.: "The Degree of Coronary Atherosclerosis in Bilaterally Oophorectomized Women," *Circulation*, 7:801, 1953.

14 Adlersberg, D., Schaefer, L. E., Steinberg, A. G. and Wang, C. I.: "Age, Sex, Serum Lipids, and Coronary Atherosclerosis," *J.A.M.A.*, 162:619, 1956.

15 Barr, D. P.: *Hormonal Factors in the Pathogenesis of Atherosclerosis.* Read at a Symposium on Arteriosclerosis at the University of Minnesota, Minneapolis, Sept. 7-9, 1955.

16 Parsons, W. B., Achor, R. W. P., Berge, K. G., McKenzie, B. F. and Barker, N. W.: "Changes in Concentration of Blood Lipids Following Administration of Large Doses of Nicotinic Acid to Persons with Hypercholesterolemia: Preliminary Observations," *Proc. Staff Meet., Mayo Clin.*, 31:391, 1956.

17 Evaluation of Serum Lipoprotein and Cholesterol Measurements as Predictors of Clinical Complications of Atherosclerosis. Report of a Cooperative Study of Lipoproteins and Atherosclerosis," *Circulation*, 14:691, 1956.

18 Enos, W. F., Holmes, R. H. and Beyer, J.: "Coronary Disease Among United States Soldiers Killed in Action in Korea: Preliminary Report," *J.A.M.A.*, 152:1090, 1953.

19 Holman, R. L., McGill, H. C., Strong, J. P., Griffin, O. R. and Geer, J. C.: *Natural History of Atherosclerosis. Scientific Exhibit.* 106th Annual Meeting of the American Medical Association. New York, N. Y. June 3-7, 1957.

20 Dublin, L. I., Lotka, A. J. and Spiegelman, M.: *Length of Life: A Study of the Life Table.* Revised Ed. Ronald Press, New York, 1949.

21 Morris, J. N., Heady, J. A. and Raffle, P. A., Roberts, C. G. and Parks, J. W.: "Coronary Heart Disease and Physical Activity of Work," *Lancet*, 2:1053, 1953.

THE ELECTROCARDIOGRAM OF THE MONTH

The authors would be pleased to receive comment and controversy from readers in relation to explanations offered.

A 55 year old woman with no known heart disease was admitted to the hospital because of a supraventricular tachycardia. She was given six grains of quinidine sulfate every two hours and when this failed to stop the tachycardia she was digitalized. The quinidine was continued. Her pulse rate then became slower but irregular and the electrocardiogram shown below was recorded at that time.

Interpretation

Lead V_1 (Figure 1) illustrates the problem most clearly. There is a regular auricular rate of 120 per minute. The first two P waves are superimposed upon the preceding T waves; they are conducted by the A-V bundle and the right bundle branch but not by the left bundle branch. The third P wave is not conducted by the A-V bundle; the fourth P wave therefore falls after the A-V bundle has had a long rest period and is conducted normally—the PR interval is short. The

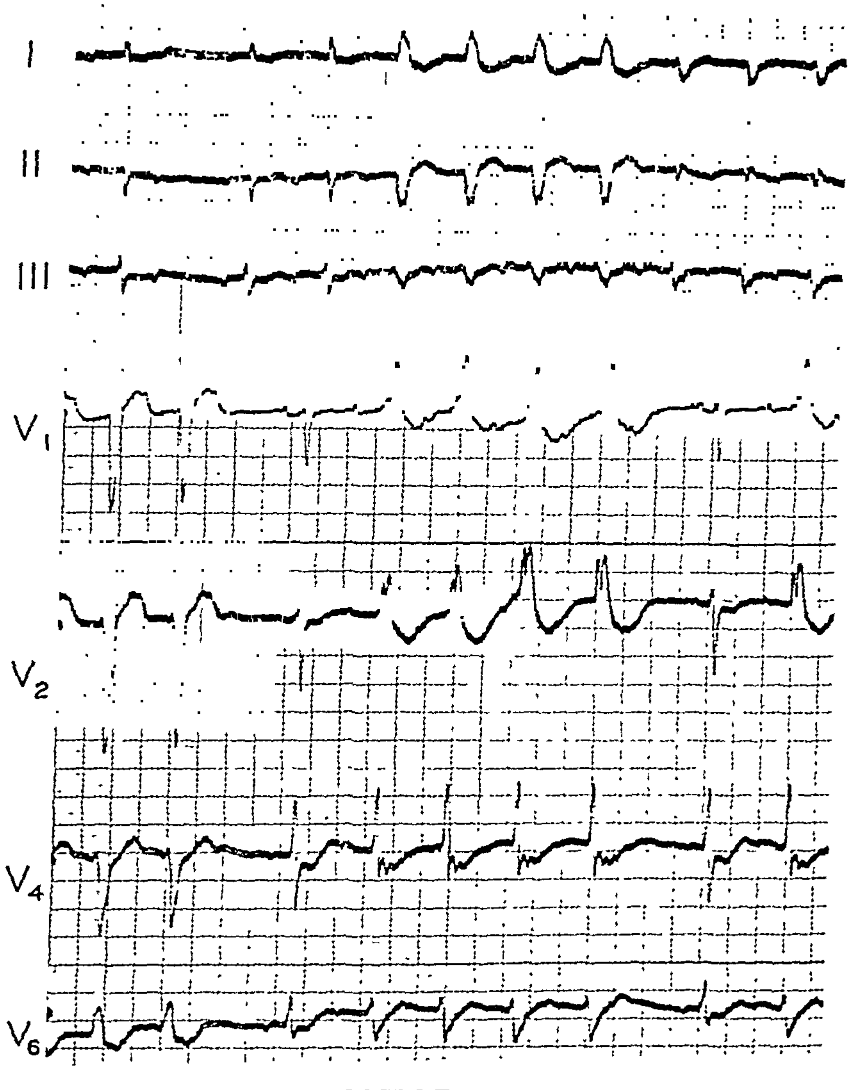

FIGURE 1

fifth, sixth, seventh, and eighth P waves are all conducted by the A-V bundle but the PR interval becomes progressively prolonged; following the ninth P wave the impulse is blocked. The QRS complexes following the fifth through the eighth P waves are of the *right* bundle branch block form. The 10th P wave follows the prolonged rest period offered by blocking of the previous beat and once again normal rapid conduction occurs in the A-V bundle (the PR interval is short).

Thus the tracing shows repeated examples of the block in the right bundle branch, of block in the left bundle branch, and of block in both bundle branches simultaneously (or in the A-V bundle itself). This condition was presumably due to the effects of digitalis and quinidine. When all drugs were discontinued the tracing returned to normal and she has had no further difficulties.

Vectorcardiograms were made (Figure 2) when conduction was normal, when the right bundle branch was blocked, and when the left bundle branch was blocked. The tetrahedron, cube and Frank frames of reference were employed. Two degrees of left bundle branch block were recorded when the horizontal loop of the cube was being examined.

MANUEL GARDBERG, M.D.
IRVING L. ROSEN, M.D.
NEW ORLEANS, LOUISIANA
Cardiac Research Laboratory, Touro Infirmary and the Department of Medicine, Louisiana State University Medical School.

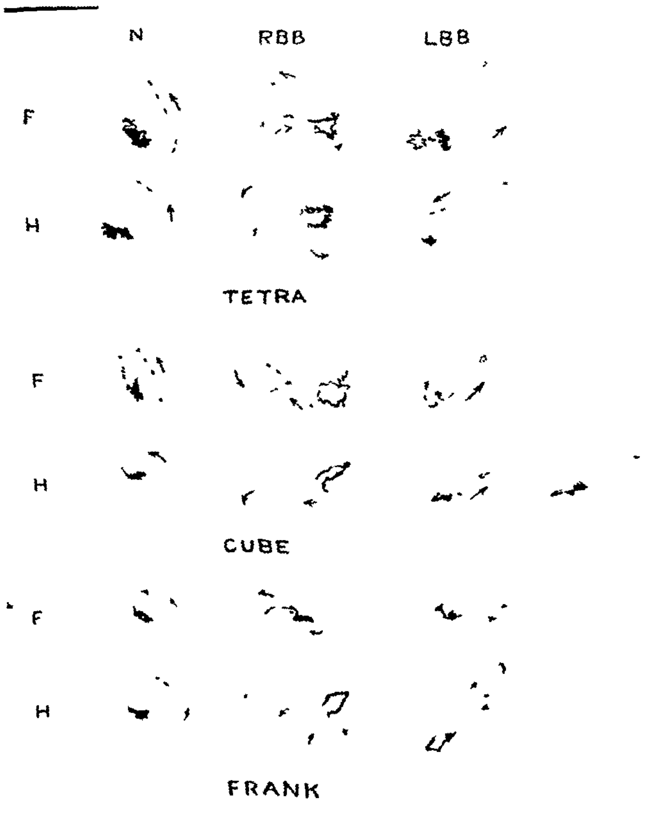

FIGURE 2

Editorial

Soldiers of Peace

During the Middle Ages, Christians and Muslims were locked in a senseless struggle for the possession of a tomb. Millions came from Europe to assault and batter and kill; millions defended and perpetrated destruction in return. In the midst of this, Richard the Lion Hearted of England fell sick. To him came the great Saladin himself disguised as a physician, seeking permission to apply his ministrations. While the henchmen of Richard rattled their sabres and sought for hidden poisons, the King of England himself had no fears. He commanded the doctor to proceed, saying that one whose task was to heal did not distinguish between friend and foe; those who were sworn to give comfort counted no aliens; for them all humanity was one for which all suffering had to be removed.

History stands witness to the fact that doctors through the ages have never known the barriers of nationality, colour or creed in the use of their art. To them all humanity had been one, and they have applied their skill and knowledge to all in an equal degree. The political creed of the medical man which existed from time immemorial is exactly the one towards which the world is now working the hard way—by learning its lessons from the ravages of world wars, by going through endless devastation—that of one humanity, one world.

The Prince of Peace is depicted in religious scriptures as a healer, for peace and healing must go together. None could be a greater champion of peace than Jesus Christ, or a better doctor to Man, working for the greatest degree of comfort not simply for the body but for the soul as well.

What is war? It is nothing but the loosing of the most evil instincts of man, an expression of his destructive genius, which results from the evils of greed, supremacy and possession, and builds for itself a justification. All these, as war itself, are in fact alien to the spirit of a doctor who dedicates himself to the task of reducing suffering.

War seeks to tear the physical being of humanity apart, bruise the body and injure the soul. The doctor forthwith sets his instruments in order and proceeds to repair what has been broken. The struggle of the surgeon in the field camp or the base hospital is not so much to join fractures, set bones, stop bleeding, save life, as it is to struggle against War itself, for fermenting war and its fever are in the last analysis, nothing but a psychosis, an unwholesome state of the mind, an ailment, often artificially engendered. But the doctor does not speak the language of the politician or the philosopher, which is taboo for him, as in the endless dogmatism of the world this language is bound to create more dissension and disrupt peace. He speaks the language of action, he struggles against the ravages of disease and devastation, he builds in the midst of destruction and his work lives. A doctor is thus a great soldier of peace.

One can well visualise the great good to humanity which can emanate if all these "soldiers of peace" put their heads together, exchange ideas and discuss the results of their significant research. It would definitely make their language of peace universal and understandable at the antipodes.

For some years past, international congresses of medical men under the auspices of the American College of Chest Physicians have been taking place at different points of the globe. They have done tremendous good towards this end; they have not only made it possible for the representatives of one nation to carry back with them the benefits of research in medical science elsewhere, but also have helped underdeveloped nations raise their standards in an effort to be on a par with the more advanced countries. In other words, the congress sessions have marked definite stages in taking the language of peace towards universality.

Healers and doctors have ever played in the past a subsidiary role in the unfolding vistas of history, in which political rivalries and an endless miasma of bloody wars have complicated tremendously the picture of a torn and bleeding world. One can only look with hope to the operation of these forces, wherein medical men play their role in an ever increasing tempo of importance.

*Mohammed Ibrahim, M.D., F.C.C.P.**
Dacca, East Pakistan

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*Governor for East Pakistan.

The President's Page

"On to Tokyo" is our slogan for 1958. Once again, we are given the opportunity to participate in an international congress. In 1950, a large group of our members met in Rome to celebrate the First International Congress on Diseases of the Chest sponsored by the American College of Chest Physicians. During the Second International Congress in 1952, some of the same physicians and their families, with many others, met in Rio de Janeiro to renew the acquaintances which were established in Rome. In 1954, the number of physicians and their families who traveled to Barcelona to celebrate the Third International Congress totalled nearly 2,000 and in 1956, the Fourth International Congress held in Cologne, Germany established a new attendance record of 2,163 physicians and their families representing 58 countries.

For the first time, we will assemble in the Orient and the advance interest expressed by our members indicates that we will have another successful congress. This congress will afford you an opportunity to meet many of your colleagues from various countries and to discuss with them questions of mutual interest.

The Japan Chapter of the College, through its committees and its active Secretary-General, is making plans to see that everyone who attends the congress will have a most enjoyable stay. They are also arranging a splendid program of entertainment in true Oriental style and I can assure you that their hospitality will be something you will always remember. Prime Minister Nobusuke Kishi, the Honorary President of the Congress, and many other Japanese dignitaries will serve as official hosts.

Following the close of the congress in Tokyo, elaborate tours have been arranged which will include visits to many of the beauty spots in Japan, Hong Kong, the Philippines, and Hawaiian Islands. The College chapters in these places are preparing interesting scientific and social programs which I am sure you will not want to miss.

The coming months promise to be busy ones, with nineteen chapter meetings in the United States scheduled between February and May. These chapters meet at the time of the annual meetings of the state medical societies and it is gratifying to note that most of the chapters have begun work on their scientific programs. A one hundred per cent membership attendance should be the goal of every chapter. To accomplish this, the program must be completed in sufficient time to provide adequate publicity and we will appreciate the continued cooperation of chapter officials in this respect. The programs presented at chapter meetings have been of high caliber and several excellent papers given at these scientific sessions have been published in the College journal. The program committees are doing a splendid job in arranging for papers on both cardiac and pulmonary problems. The increase in attendance at our chapter meetings is a compliment to those who have given time and effort to the organization of these programs.

Our chapters provide worthwhile opportunities for members to become familiar with the objectives of the College and many physicians who have participated in chapter work move on to activities at the national level. We are counting on the cooperation of all members in making the 1958 chapter meetings more successful than ever.

We, of course, must not forget our 24th Annual Meeting to be held in San Francisco, June 18-22. Your energetic Program Committee is organizing excellent scientific sessions which I am sure will measure up to the high standards of College meetings. If you plan to attend the Annual Meeting, I would urge you to obtain your hotel reservations immediately. You will find a coupon for obtaining reservations on page xxix of this issue.

Burgess L. Gordon

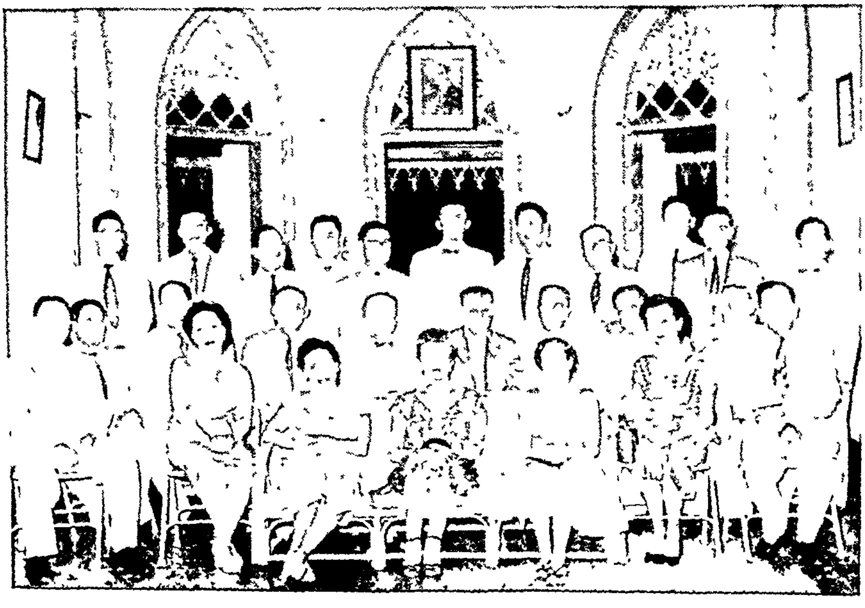
POST-CONGRESS TOUR

Following the close of the Congress in Tokyo, a group of physicians and their families will travel to Hong Kong where the Hong Kong and China Chapter of the College will present a scientific and social program. It is planned to have a series of Fireside Conferences where the members of the Hong Kong and China Chapter can meet the visiting physicians and discuss scientific projects of mutual interest. This will be followed by the presentation of formal papers by invited guests and members of the chapter and there will be a general discussion of the papers presented. Dr. Li Shu Fan, Regent of the College in Hong Kong, is planning a social program for the physicians and their families.

COMMITTEE ON NOMINATIONS

Elections for offices which will expire in June, 1958, will be held at the Fairmont Hotel, San Francisco, on Saturday, June 21. Recommendations for elective offices may be addressed to the chairman of the Committee on Nominations, Dr. J. Winthrop Peabody, Sr., 1746 K Street, N. W., Washington, D. C. The other members of the committee are Dr. Sumner S. Cohen, Oak Terrace, Minnesota and Dr. Orin J. Farness, Tucson, Arizona.

CHAPTER ORGANIZED IN THAILAND



The 69th chapter of the American College of Chest Physicians was organized in Bangkok, Thailand, on October 31, 1957, with 20 charter members. The following officers were elected:

President:	Prasert Kangsadal, Dhonburi
Vice-President:	Smarn Muntarbhorn, Bangkok
Secretary-Treasurer:	Sombun Pongaksara, Bangkok

The Governor of the College in Thailand is Dr. Thip Pholpoke, Bangkok.

A cocktail party was given in honor of Mr. and Mrs. Murray Kornfeld at the Medical Association Building in Bangkok on Wednesday evening, October 30.

CHAPTER ORGANIZED IN EAST PAKISTAN

Members of the College in East Pakistan met in Dacca on October 27 to organize the East Pakistan chapter. Speakers on the program were Drs. Mohammed Ibrahim, Governor of the College for East Pakistan, M. A. Mannan, H. Rahman, T. Hossain, and K. A. Khaleque. The following officers were elected:

President: Mohammed Ibrahim, Dacca
Vice-President: Hammadur Rahman, Dacca
Secretary-Treasurer: Abdul Mannan, Dacca

EAST PAKISTAN CHAPTER
AMERICAN COLLEGE OF CHEST PHYSICIANS

College Chapter News

NEW YORK STATE CHAPTER

The 18th clinical meeting of the New York State Chapter will be held in New York City, February 20-21. The Hotel Commodore will be the headquarters hotel. The following program will be presented:

February 20 *Hotel Roosevelt*
Motion Picture Session—Open Heart Surgery
Chairman: Francis O'Donnell, Jr., Buffalo, President, New York State Chapter
8:00 p.m. "Medical Aspects"
Irving G. Kroop, Brooklyn
"Surgical Aspects"
Philip Crastnopol and Alvin A. Bakst, Brooklyn

February 21 *New York Medical College, Metropolitan Hospital Medical Center*
Chairman: Francis O'Donnell, Jr., Buffalo
9:00 a.m. 'The Formation of a Gastric Tube to By-pass or Replace Obstructing Lesions of the Esophagus"
James M. Winfield and Henry Heimlich, New York City
"Buccal Enzyme Therapy in Acute and Chronic Respiratory Tract Infections"
Irving Innerfield, Harold Shub, and Linn J. Boyd, New York City
"Mucoviscoidosis"
Edward Wasserman and Lawrence Slobody, New York City
"Clinical Application of Tracheal Fenestration"
E. Ernest Rockey, New York City
"Some New Aspects of Experimental Cardiovascular Necrosis"
David Lehr, New York City
"Pneumoconioses in New York State Today"
Morris Kleinfeld, New York City

12:15 p.m. Luncheon
Welcome address: Ralph E. Snyder, Dean, New York Medical College and Flower-Fifth Avenue Hospital; Ferdinand Piazza, Medical Superintendent, Metropolitan Hospital Medical Center, New York City
2:00 p.m. Chairman: Emil J. Naclerio, First Vice-President, New York State Chapter, New York City
"Acute Cor Pulmonale"
David Scherf, New York City
"Management of Patients with Angina Pectoris" (Panel)
Moderator: Linn J. Boyd, New York City
Panel: Simon Dack, Harry Leinoff, and Samuel A. Thompson, New York City
"Asthma in Children and its Complications"
Samuel Untracht, New York City
"Clinical Indications for Aortography and its Complications"
Joseph R. Wilder, New York City
"Cycloserine in the Treatment of Pulmonary Tuberculosis"
Israel G. Epstein, Brooklyn
"Steroids in the Treatment of Pulmonary Tuberculosis"
Paul K. Bornstein, Asbury Park, New Jersey

NEW CHAPTER OFFICERS

LOUISIANA CHAPTER

President: Frank W. Pickell, Baton Rouge
Vice-President: Morton M. Ziskind, New Orleans
Secretary-Treasurer: Howard A. Buechner, New Orleans (re-elected)

College News Notes

Dr. Thomas G. Baffes, Skokie, Illinois, has been selected by the U. S. Junior Chamber of Commerce as one of America's Ten Outstanding Young Men of 1957, for his work in developing the first surgical technique of transposition of the great vessels in the hearts of infants.

The following Fellows of the College will present lectures at the Chicago Medical Society's Clinical Conference to be held at the Palmer House, Chicago, March 4-7: **Drs. Alvan L. Barach**, New York City; **Ethan Allan Brown**, Boston; **George E. Burch**, New Orleans, and **Richard H. Chamberlain**, Philadelphia.

CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

24th Annual Meeting, American College of Chest Physicians
Fairmont Hotel, San Francisco, June 18-22, 1958

Fifth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Tokyo, Japan, September 7-11, 1958

POSTGRADUATE COURSES

11th Annual Postgraduate Course on Diseases of the Chest
Warwick Hotel, Philadelphia, March 3-7, 1958

4th Southern Postgraduate Course on Diseases of the Chest
Grady Memorial Hospital, Atlanta, Georgia, March 10-15, 1958

CHAPTER MEETING

Clinical Meeting, New York State Chapter, New York City
February 20-21, 1958

ANNUAL MOTION PICTURE PROGRAM

The Committee on Motion Pictures of the College is preparing a program of motion pictures dealing with diseases of the chest to be presented at the 24th Annual Meeting to be held in San Francisco, June 18-22. Physicians who have interesting films are invited to send all pertinent information, i.e., brief description, color or black and white, silent or sound, running time, etc., to the committee for consideration. Please address your letters to: Dr. Paul H. Holinger, Chairman, Committee on Motion Pictures, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Book Reviews

DISEASES OF THE CHEST, *by* H. Corwin Hinshaw, M.D., Ph.D. and L. Henry Garland, M.B., B.Ch. *W. B. Saunders Company, Philadelphia and London, 1956,* $15.00.

This volume of 727 pages is an excellent presentation of the entire field of diseases of the chest. It is composed of 40 chapters beginning with diagnostic procedure and carrying through all worthwhile treatment and preventive measures. Emphasis is placed on diagnosis as the cornerstone with the numerous special diagnostic procedures now available. Four entire chapters are devoted to diagnosis.

The chapter on "Segmental Anatomy of the Trachea, Bronchial Tree and Lung" emphasizes the importance of such information both in diagnosis and treatment, particularly surgical resection. Measurements of pulmonary function are also given a prominent place.

There are seven chapters, consisting of a total of 130 pages, on various aspects of tuberculosis. Pneumonia, pulmonary fungus infections, tropical pulmonary diseases, and numerous other important conditions are presented. A final excellent chapter is devoted to pulmonary diseases of occupational origin.

Antimicrobial drugs, including chemicals and antibiotics, are presented as they are indicated for various diseases, as well as surgical procedures developed in recent years.

The authors intentionally made the text brief but included reference lists of more recent publications to aid those who desire to do additional reading. The volume is profusely illustrated and contains a good index.

This book is highly recommended to physicians everywhere.

J. Arthur Myers, M.D.

LYMPHATICS, LYMPH AND LYMPHOID TISSUE, by J. M. Yoffey, M.D. and F. C. Courtice, M.D. Harvard University Press, Cambridge, Massachusetts, 1956, 510 pages, $10.00.

The subjects presented in this volume have an important bearing on clinical medicine in the daily practice of those specializing in diseases of the chest. The text contains an amazing collection of basic information supported by extensive research studies carried out by the authors. Also, it carries critically chosen, well-coordinated cardinal data derived from pertinent investigations of others. The material offered reflects the thoroughness and competence with which the authors approached their problem. Controversial and unsolved problems are considered with impartial objectivity. Illucidating tables, graphs, diagrams and pictorial illustrations are plentiful and greatly enhance the instructive value of the book. References at the end of chapters are well selected and may serve as useful guides for further orientation. Discussion of the experimental and clinical application of radioactive isotopes, the inclusion of items, such as pulmonary edema, pleural effusion, the detailed portrayal of physiologic pulmonary catharsis, the description of potential routes of lymphogenous spread of infections deserve special mention. Due attention is paid to pathways leading to sites of the Troisier-Virchow sentinel nodes. Ample space is devoted to the discussion of the clinical significance of lymphocytes.

This book is characterized by the ideal attributes of fundamental contributions to the intelligent and prudent practice of medicine; therefore, it is highly recommended to all concerned.

Andrew L. Banyai, M.D.

DISEASES of the CHEST

VOLUME XXXIII MARCH, 1958 NUMBER 3

Recent Advances in Bronchography*

JOHN E. RAYL, M.D., F.C.C.P.** and DANIEL E. SMITH, M.D.***
Oteen, North Carolina

Recent advances in bronchography have occurred as a result of new bronchographic media and technique. These advances have improved the quality of bronchography to such an extent that small bronchial lesions are more readily seen. A method of correlating these bronchographic defects with their histological appearance has increased our knowledge of the significance of these defects. The first part of this paper will discuss the recent advances in bronchographic media and technique and the second portion will describe the finer bronchographic defects and their histological appearance.

PART I

Bronchographic Media and Technique

There are two schools of thought in regard to the type of bronchogram which is considered the most valuable from a diagnostic viewpoint. The first school maintains that a good bronchogram should demonstrate patency between the trachea and the alveoli of each segment; that is, they seek alveolar filling to demonstrate this patency. Those belonging to the second group prefer to have the bronchial tree well outlined with a uniform coating from the trachea to the bronchioles without alveolar filling. Residues remaining in the lung after bronchography, whether opaque or non-opaque, can produce foreign body reactions. Foreign body reaction has been demonstrated due to the non-opaque peanut oil in Dionosil Oily,[1]† to carboxymethyl cellulose in Dionosil Aqueous[2]† and to the residual oil following instillations of Iodochlorol,[3]‡ as well as Lipiodol.[4]§ This reaction is much greater in areas where there are larger amounts of alveolar filling.[2] To avoid foreign body reaction in the lungs of patients. a technique of bronchography and a type of bronchographic medium must be used which do not produce alveolar filling. Alveolar filling is not essential for a thorough examination of the bronchial tree by bronchography.

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*From Veterans Administration Hospital, Oteen, North Carolina.

**Assistant Chief, Surgical Services and Chief, Thoracic Surgical Division.

***Chief, Broncho-Esophagology Division and Assistant Chief, Thoracic Surgical Division.

†Glaxo Laboratories Ltd., Greenford, England

‡G. D. Searle and Company, Chicago, Illinois

§E. Fougera and Company, New York, New York

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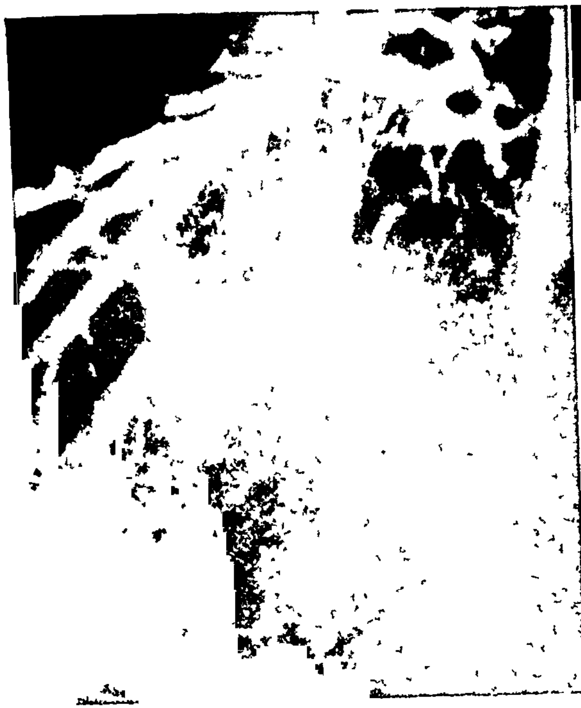

FIGURE 1

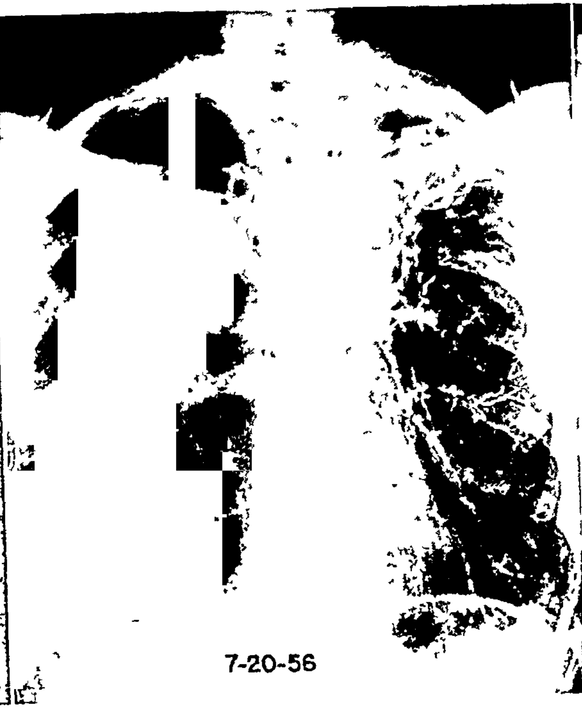

FIGURE 2

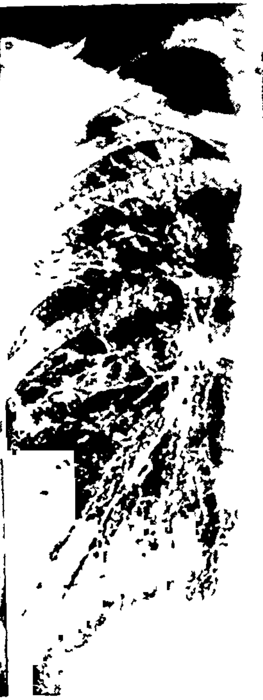

FIGURE 3A

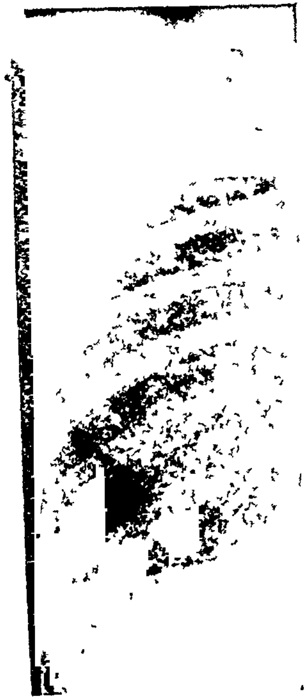

FIGURE 3B

Figure 1: Filling Beyond Areas of Obstruction. A benign tumor in the common basal stem bronchus produced sufficient obstruction to cause intermittent basilar pneumonitis and acute recurring bronchitis.—*Figure 2: Metras Catheter Used in Routine Bronchography.* To facilitate filling of apical cavities or spaces, the Metras catheter is used to fill the space before the catheter is withdrawn to allow completion of the unilateral bronchogram. This patient has a persistent apical space following a previous pulmonary resection for pulmonary tuberculosis.—*Figure 3: Residual Oil Remaining in the Lungs After Dionosil Oily Bronchogram.* Plain peanut oil in Dionosil Oily was substituted with iodinated peanut oil (Iodochlorol) for a right bronchogram so that after absorption of propyliodone, the oil remaining in the lungs can be seen on the roentgenogram. (*A*) Notice the residual oil on the roentgenogram taken twelve days later. (*B*) This residue is greater than is usually seen after Visciodol. Presence of oil remaining in the lungs after the use of Dionosil Oily has also been confirmed histologically.[1]

Alterations in the viscosity and surface tension of Lipiodol produced by the addition of sulfanilamide powder, that is Visciodol, permits a continuous and uniform coating of the entire bronchial tree with minimal alveolar filling. These outlines show good contrast in areas of pulmonary disease and usually produce a double contrast effect which permits small bronchial lesions to be readily seen. We have had no great difficulty in peripheral filling of diseased bronchi or filling beyond areas of partial obstruction (Figure 1) unless these bronchi are filled with mucopurulent secretions. Visciodol, being a more viscous medium than the Dionosils or ordinary iodized oils, flows slower through the small bronchi; therefore sufficient time must be allowed for adequate bronchial filling.

Allergic reactions in the form of uticaria by sulfanilamide powder occurred in only two patients after 500 bronchograms and these have responded well to antihistaminic therapy. Other types of postbronchographic reactions were less frequent with Visciodol than with Dionosil Oily. Bronchograms of diagnostic quality with outlining of all segments in each lung were obtained in 78 per cent of examinations with Dionosil Oily as compared to 89 per cent with Visciodol. This increase of approximately 10 per cent in the incidence of bronchograms with greater diagnostic value warrants the continued use of Visciodol. Bronchography at our hospital is used in the preoperative work-up in a large percentage of the patients prior to pulmonary resection. Experience with Visciodol now exceeds 500 examinations with excellent results.

The technique of selective bronchography using the Metras or Thompson catheters[5] to fill specific segmental bronchi is of value in the occasional case where a segment was not outlined on a previous examination. When difficulty in filling a small apical space, cavity or diseased bronchus is anticipated, the selective technique is suggested in which an appropriate Metras or Thompson catheter is used to fill this defect. The catheter is then withdrawn sufficiently to permit completion of the routine unilateral bronchogram (Figure 2) thus obviating the need for a repeated examination. Since this technique may be associated with an increase in alveolar filling, it is essential that a medium be used, such as Visciodol, which has little tendency to flow into the alveoli.

Following bronchography an aerosol using a bronchodilator drug, such as Vaponefrin,* prior to postural drainage was studied to determine its effect on the elimination of bronchographic media. Postural drainage was routinely performed three times on the day of bronchography and again the following morning. Residual oil remaining in the lungs after 72 hours following bronchograms with Dionosil Oily was determined roentgenographically by substituting iodinated peanut oil for the plain peanut oil in this medium. The use of the bronchodilator drugs after installations of Visciodol produce an 18 per cent reduction in the number of patients having significant amounts of residual oil in the lungs. The bronchodilator drugs had a similar reducing effect on the residual oil following Dionosil Oily installations. Of further interest is the fact that the opaque oil remaining in the lungs after Visciodol is less than the non-opaque oil following bronchography with Dionosil Oily (Figure 3).

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*Vaponefrin used in this study was donated by the Vaponefrin Company, Upper Darby, Pennsylvania.

PART II

Interpretation of Bronchographic Lesions

The fact that the findings on histological examination are not always consistent with the clinical opinion has necessitated a better method of clinico-pathologic correlation of areas with bronchial disease. Bronchiectasis has been studied previously by obtaining corrosion specimens; however, this prevents histological examination of the same areas. Others have studied bronchographic lesions by injecting the surgical specimen with opaque media and have taken roentgenograms of the injected specimens. This method allows the correlation of a bronchogram with the surgical specimen but it is often difficult to accurately localize a bronchial lesion for histological examination. If the surgical specimen is injected under controlled pressure with an opaque medium which solidifies during formalin fixation of the specimen, the segmental planes can then be dissected prior to roentgenographic study. The bronchus more nearly maintains its original size so the roentgenograms can be correlated segment by segment with the bronchogram for accurate localization of bronchial lesions (Figure 4). A medium now used for injection studies of this type

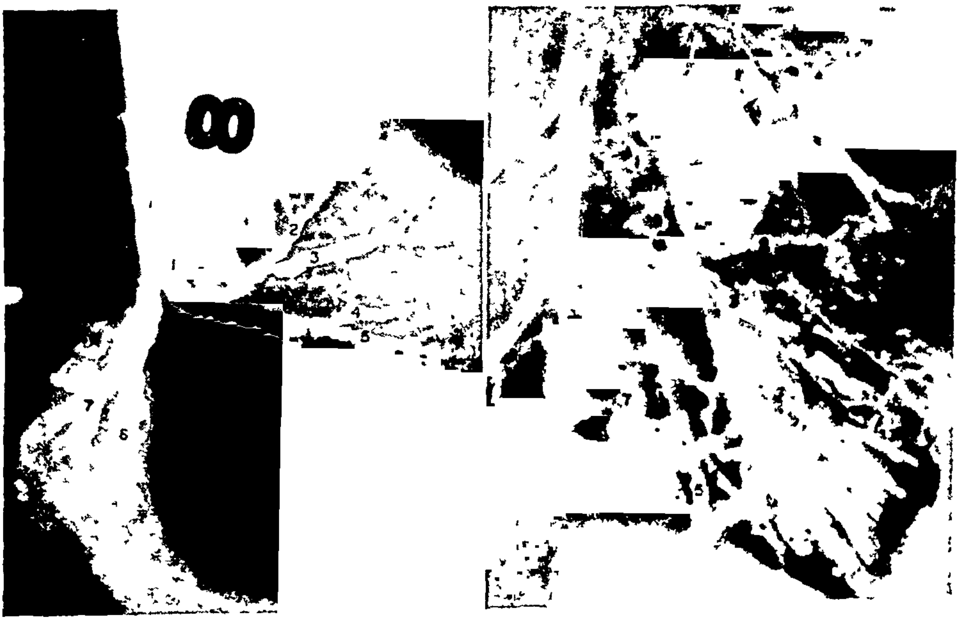

FIGURE 4A FIGURE 4B

Figure 4: Bronchogram and Injected Surgical Specimen. After left lower lobectomy, each segment is injected with an opaque medium which solidifies during formalin fixation. The segments are then separated and a roentgenogram made. This allows localization of bronchial defects for histological examination. The anteromedial basal segment (*A*) is compared with the lateral view of the preoperative bronchogram (*B*). The numbers on the bronchial branches correspond in each of the two illustrations. Only by this method could the location of such a defect be positively identified.

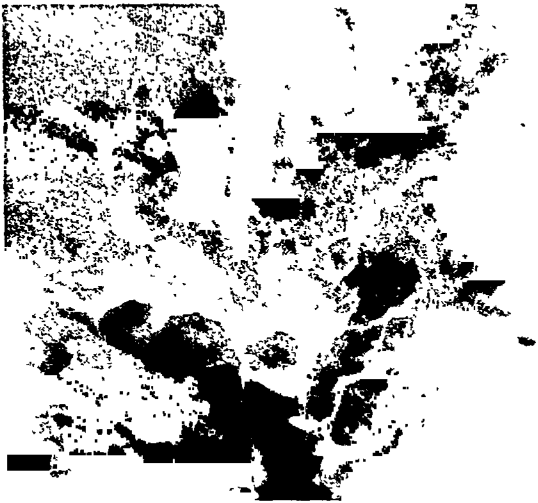

FIG. 5A

Figure 5: Inspiration and Expiration Bronchograms Showing Variation in Size of Saccular Tuberculous Bronchiectasis. Variation in size of saccular bronchiectasis in the right upper lobe is seen on lateral bronchogram in (*A*) inspiration and (*B*) expiration. A histological section from the posterior segmental bronchi is seen in Figure 6.

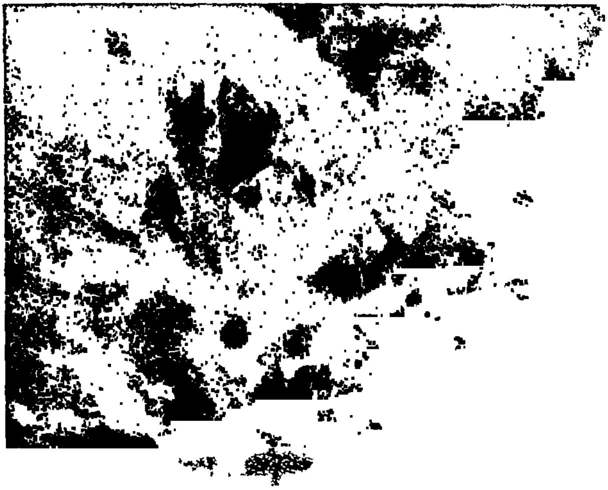

FIG. 5B

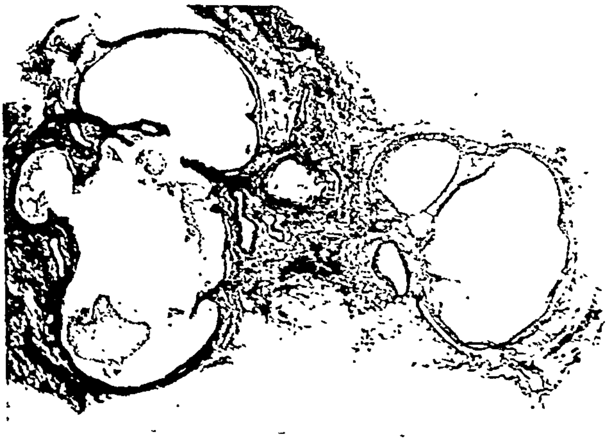

FIGURE 6: *Histology of Saccular Bronchiectasis Which Changes in Size During Respiration.* A thin layer of fibrous tissue and smooth muscle surrounds the dilated bronchi. Blood vessels are surrounded by greater amount of fibrosis. No active inflammatory reaction is seen. Massen Stain, 4x.

is made by mixing Lipiodol, egg yolk and acacia in appropriate amounts for the desired consistency. Studies of this nature increase the diagnostic potentialities of bronchial defects so adequate treatment can be made more effective.

Normal variation in the caliber of the bronchi can be observed on bronchograms taken during inspiration and expiration. Bronchi which show saccular dilatation (Figure 5) on inspiration but are markedly reduced in size during expiration usually show little or no evidence of inflammatory

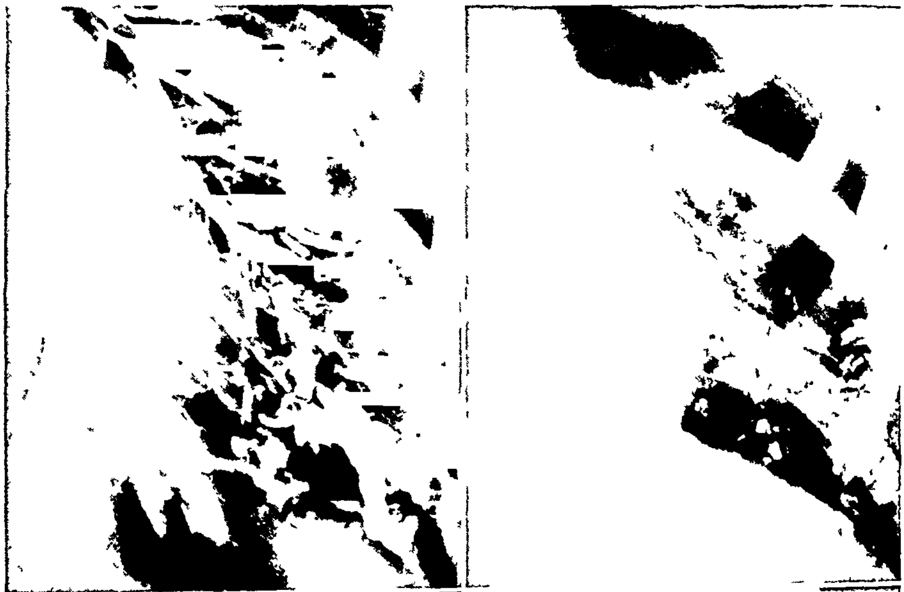

FIG. 7A

FIG. 7B

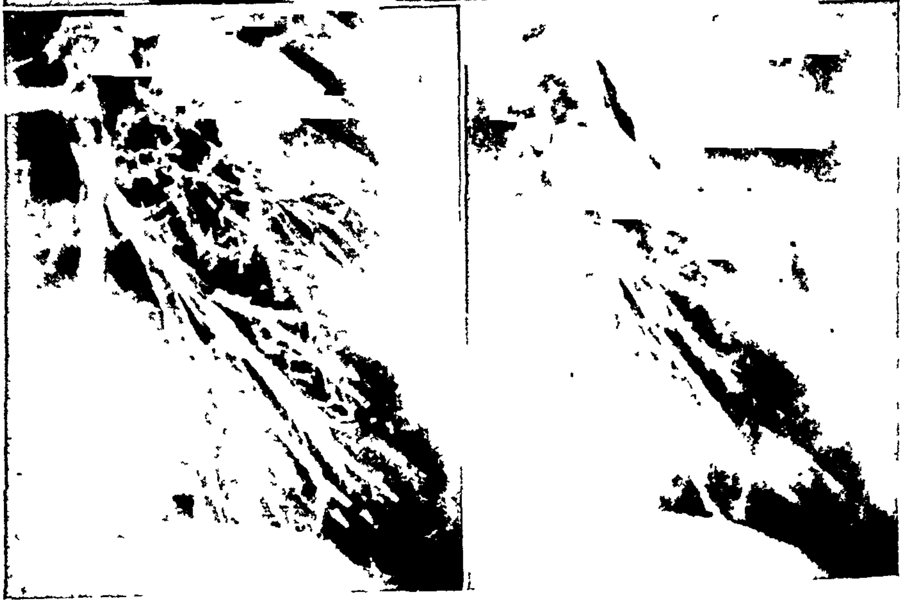

FIG. 8A

FIG. 8B

Figure 7: Outline of Bronchi in Areas of Bronchiectasis on 24-Hour Roentgenogram. (*A*) Bronchiectasis in left lower lobe is seen on bronchogram. (*B*) An outline of the bronchiectatic bronchi still present on the 24-hour roentgenogram shows evidence of poor bronchial cleansing.—*Figure 8: Normal Left Bronchogram with 24-Hour Bronchial Outline.* (*A*) Bronchogram left lower lobe shows normal outlines of bronchi. (*B*) Roentgenogram in 24 hours shows outline of two basal segments. Histological sections of one of these bronchi are seen in Figure 9.

reaction or fibrosis on histological examination (Figure 6). Bronchi which do not vary in size during the two phases of respiration more frequently show inflammatory changes or significant amounts of fibrous tissue in the bronchial wall. Roentgenograms are routinely taken in one view during the two respiratory phases in order to correlate these findings with histological sections.

Histological findings in early chronic bronchitis[6] consist of hypertrophy of the mucous-secreting elements which is corroborated by an excess of

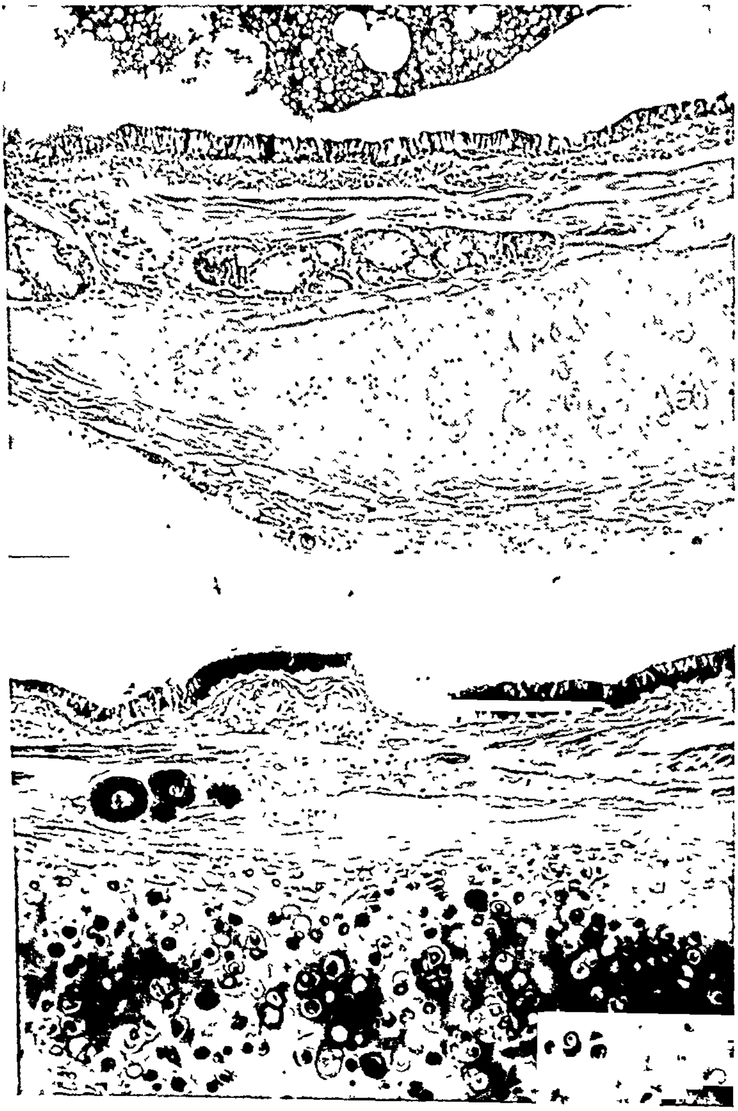

FIGURE 9A

FIGURE 9B

Figure 9: Histology of Bronchus Showing 24-Hour Outline. The basal bronchus outlined on the 24-hour roentgenogram in Figure 8B shows numerous goblet cells in the epithelium. (*A*) Hematoxylin and Eosin stain. (*B*) Periodic acid-Schiff stain is more specific for mucus. (67x)

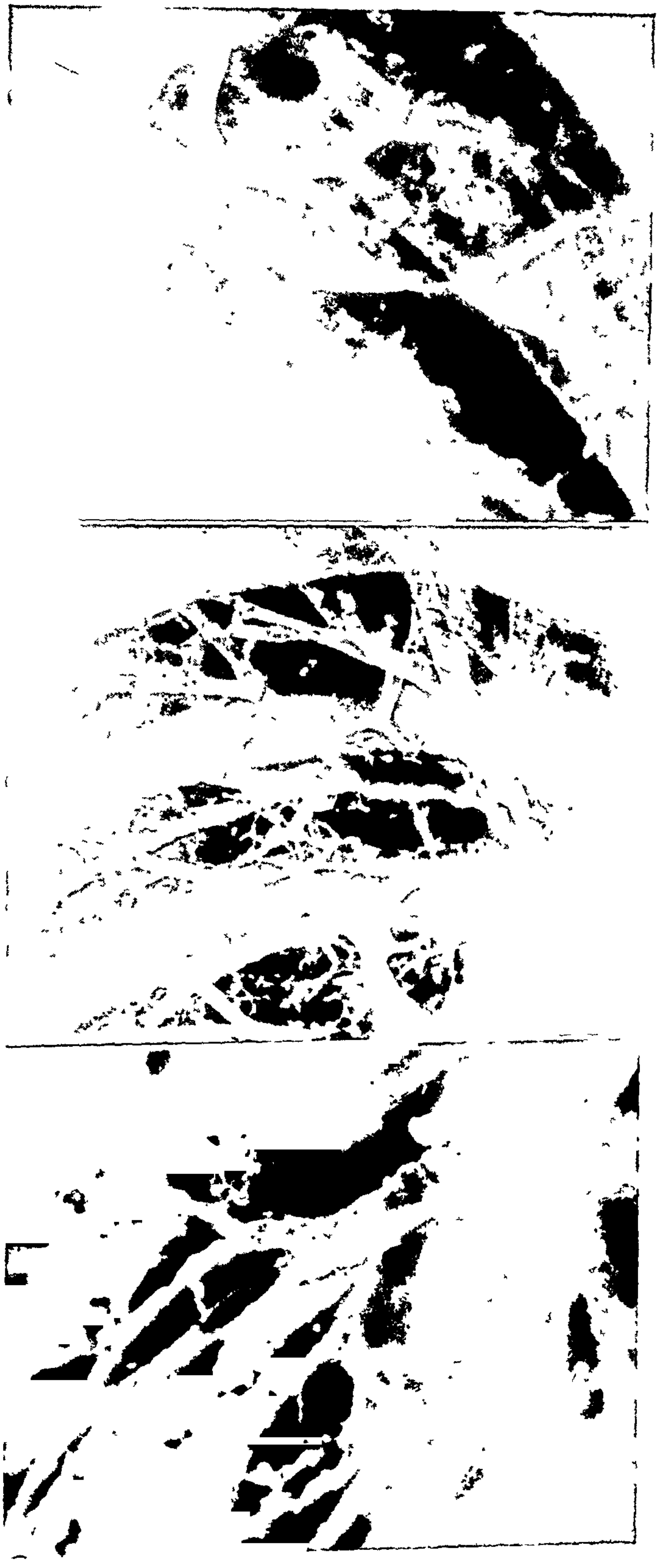

FIG. 10A

FIG. 10B

Figure 10: Bronchographic Changes in Early Chronic Bronchitis. (*A*) Wavy outlines of lingular bronchi; (*B*) Rippled appearance of the right upper lobe bronchi and (*C*) Transverse striations in the right middle lobe and basal segmental bronchi.

FIG. 10C

mucus in the air passages. These changes consist of an increase in the number of goblet cells in the epithelial surface and hypertrophy of the mucous glands with marked dilatation of their ducts. When an excess of mucus is present in the bronchi, the cilia exert little more than a churning action[7] on the mucus which steadily accumulates in the lungs requiring cough for evacuation. The resistance-lowering action of mucus together with purulent bronchiolitis and its sequela lead to progressive obliteration of pulmonary tissue thus setting the stage for production of emphysema.[6] In order to treat chronic bronchitis and prevent the progressive changes in the lungs, a definite diagnosis must be made in the early stage of this disease.

Outlines of the bronchial tree with bronchographic medium as seen on a subsequent roentgenogram (Figure 7) have been observed in the areas of bronchiectasis since the early days of bronchography. This has been attributed to a poor cleansing mechanism of the diseased bronchi. In chronic bronchitis one of the earliest changes which occurs in the bronchus is an impaired cleansing ability. This is apparent in a bronchus which appears normal on the bronchogram (Figure 8) but remains outlined on a roentgenogram in 24 hours. The only changes on histological examination of this bronchus (Figure 9) is an increase in goblet cells in the epithelium and a few inflammatory cells in the submucosa. A roentgenogram taken 24 hours after bronchography is extremely valuable to observe this cleansing mechanism. When bronchial outlines are observed, a closer examination of the bronchogram will frequently reveal less obvious structural changes in the walls of these bronchi.

In 1949 DiRienzo[8] and in 1953 Simon and Galbraith[9] have described

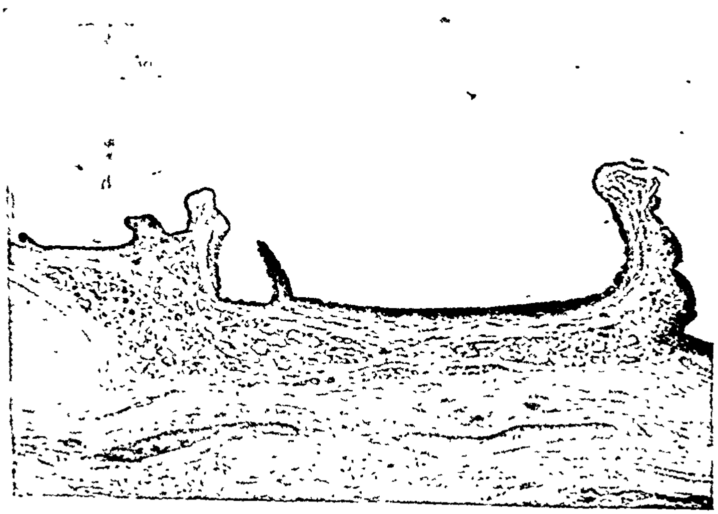

FIGURE 11: *Transverse Striations of Bronchial Mucosa In Chronic Bronchitis.* Longitudinal histological section (H&E Stain) of a bronchus shows transverse striations of the bronchial mucosa. Presence of inflammatory cells in the submucosa are consistent with a diagnosis of chronic bronchitis. The mucosal projections sometimes contain small bundles of smooth muscle.

some of the bronchographic findings in patients having chronic bronchitis. The use of Visciodol permits a more detailed study of these lesions so that a diagnosis can be made before more advanced changes occur. Bronchographic changes in early chronic bronchitis may consist either of wavy

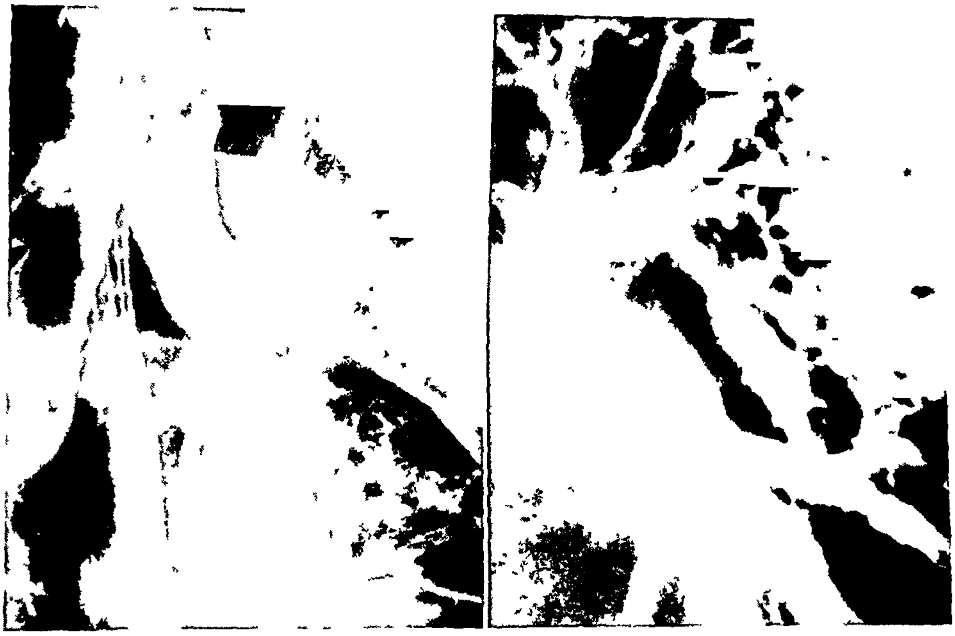
FIGURE 12A FIGURE 12B

Figure 12: Bronchographic Changes in Chronic Bronchitis Producing Diverticula. (*A*) Bronchial diverticulae seen in patients with chronic bronchitis may present a "saw-toothed" appearance, or (*B*) they may be so numerous that they produce "feathering" of the bronchial outline.

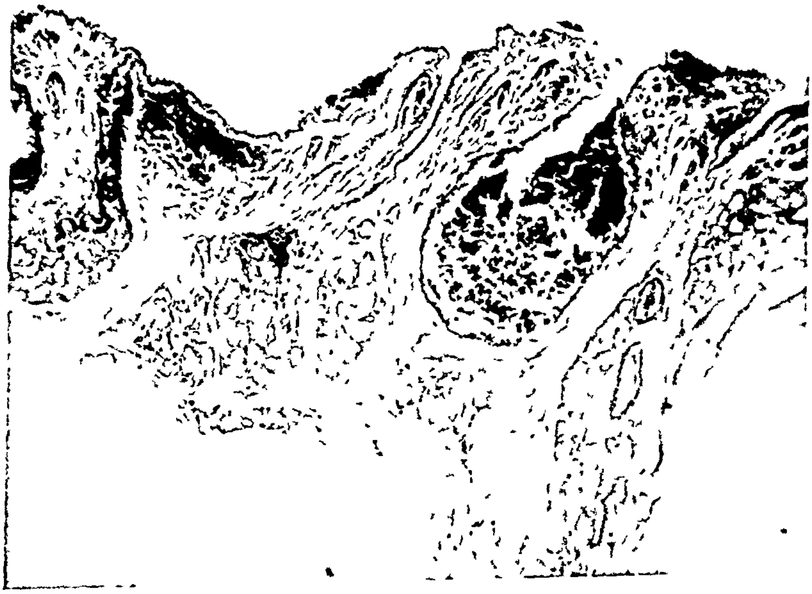

FIGURE 13: *Histology of Diverticula.* Two large dilated ducts of mucous glands are seen containing blood. Portions of three other ducts are seen with less evidence of dilatation. Hypertrophy of the mucous glands is evident.

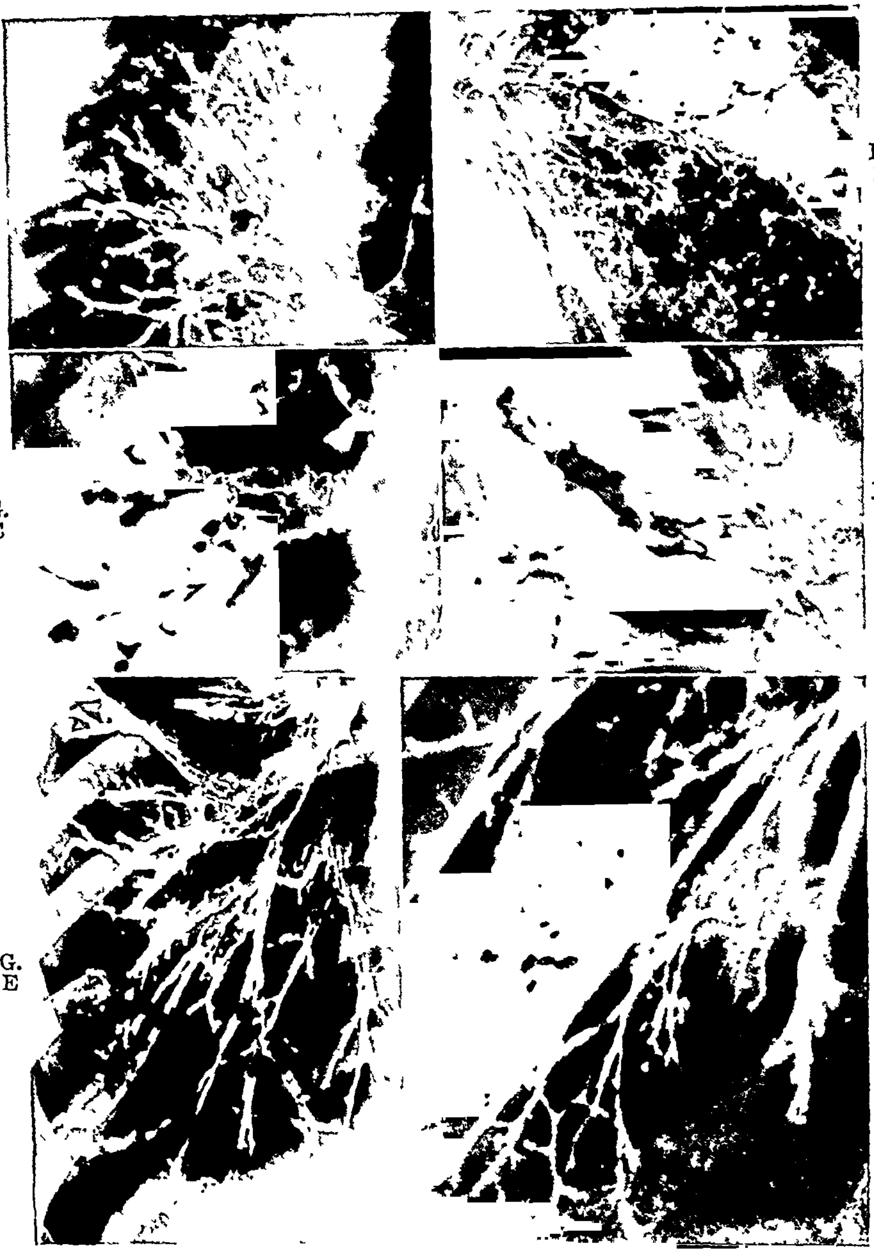

Figure 14: Bronchographic Changes in Advanced Chronic Bronchitis. (*A*) Cylindrical bronchiolectasis is evident in the right upper lobe when dilated bronchi approach the lung periphery; (*B*) Cystic bronchiolectasis is present in the left anterior segment; (*C*) Cylindrical and cystic bronchiectasis is present in a right upper lobe bronchus; (*D*) Diverticula are seen in a right upper lobe bronchus; (*E*) Areas of constriction and dilatation are seen in the right basal segments of a patient with secondary emphysema, and (*F*) "Pipe-stem" deformity of a right basal segmental bronchus is characterized by very little diminution in size of the bronchus.

outlines of the bronchi showing alternate areas of dilatation and constriction or of a rippled appearance (Figure 10). These areas of constriction and dilatation may vary in length and diameter. When the interval between them is small, transverse striations in the bronchial mucosa are prominent (Figures 10 and 11).

Associated with chronic bronchitis, one will occasionally notice small diverticula along the surface of the larger bronchi measuring up to three millimeters in diameter. These diverticula may be few or numerous. They may have the appearance of feathering along the edge of the bronchial wall or may have a saw-toothed appearance (Figure 12). Bronchial diverticulosis was first described by Morlock and Pinchin[10] in 1933, but it was not until 1953 that Duprez and Mampuys[11] showed that these diverticula were dilated ducts of the bronchial mucous glands (Figure 13). Irregularity of the transverse striations will occasionally show filling defects which simulate diverticula in the bronchogram.

Bronchographic lesions become more prominent (Figure 14) in later stages of chronic bronchitis. Bronchioles in the periphery of the lung

FIGURE 15: *Bronchographic Changes in Bronchitis Which Simulate Bronchiectasis.* An acute respiratory infection in a patient with chronic bronchitis produces changes in the basal segments of the left lower lobe which simulate bronchiectasis. Histological section of the posterior basal bronchus is seen in Figure 16.

may become dilated and show cylindrical or cystic bronchiolectasis. Medium sized bronchi may also show similar cylindrical and cystic dilatations. Cystic dilatations are due to destruction of the wall by localized areas of acute inflammation. Diverticula may appear along the walls of the medium sized bronchi. After the clinical symptoms of emphysema begin to appear, the basal bronchi may show areas having marked constriction of the lumen with distal dilatations or they may extend some distance without variation in the caliber of the lumen.

Bronchitis following an acute respiratory infection may produce such severe changes that a diagnosis of bronchiectasis is frequently made. This change was demonstrated by Blades[12] in patients with so-called atypical pneumonia. More often this is seen in patients with chronic bronchitis due to superimposed acute infection (Figure 15). On histological examination the bronchi show acute suppurative bronchitis (Figure 16). Bronchographic changes in acute bronchitis may be differentiated from those seen in true bronchiectasis by their symmetrical areas of dilatation and constriction, by relatively slight variation in the diameter of the bronchi and frequently by changes in other bronchi consistent with chronic bronchitis. Bronchial deformity produced primarily by atelectasis gives a similar appearance except the lumen decreases in diameter more rapidly due to relaxation and relative shortening of the bronchus. The nature of sputum

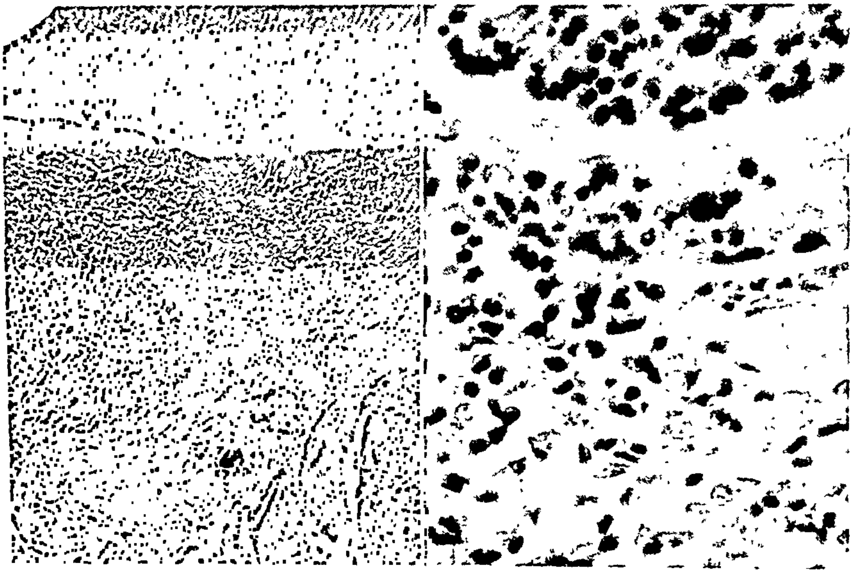

FIGURE 16A FIGURE 16B

Figure 16: Histology of Acute Bronchitis. Histological section of the posterior basal bronchus of the left lower lobe seen in Figure 15 shows acute suppurative bronchitis without fibrosis. (*A*) Acute and chronic inflammatory cells are seen in the bronchial wall and lumen. A lymph follicle is also seen (80x). (*B*) The epithelial layer is infiltrated with similar inflammatory cells. The smooth muscle fibers are separated by edema. There is no evidence of fibrosis or destruction of the bronchial wall to suggest bronchiectasis.

and the bronchoscopic findings are often helpful in differentiating these bronchial lesions.

A poor prognosis can be anticipated if we attempt to cure patients with chronic bronchitis by surgical excision of the more involved areas, unless we use intensive medical therapy during the immediate preoperative and postoperative periods. Following surgery these patients must continue indefinitely under good medical management. Some patients who receive adequate medical treatment may not require surgery (Figure 17). It is imperative that a bronchogram be inspected closely especially to observe the less obvious changes which are consistent with chronic bronchitis prior to surgical treatment.

CONCLUSIONS

1. Since all bronchographic media remaining in the alveoli may produce foreign body reaction, it is recommended that a technique of bronchography and a type of bronchographic medium be used in which alveolar filling is not seen. There is less alveolar retention after Visciodol than after other bronchographic media.

2. The technique of selective bronchography using the Metras catheters is of value when there is insufficient outlining of a particular segment during a previous bronchographic examination. Routine bronchography in selected cases using an appropriate Metras catheter prevents the necessity of repeated bronchograms.

3. A method for correlating bronchiographic defects with their histo-

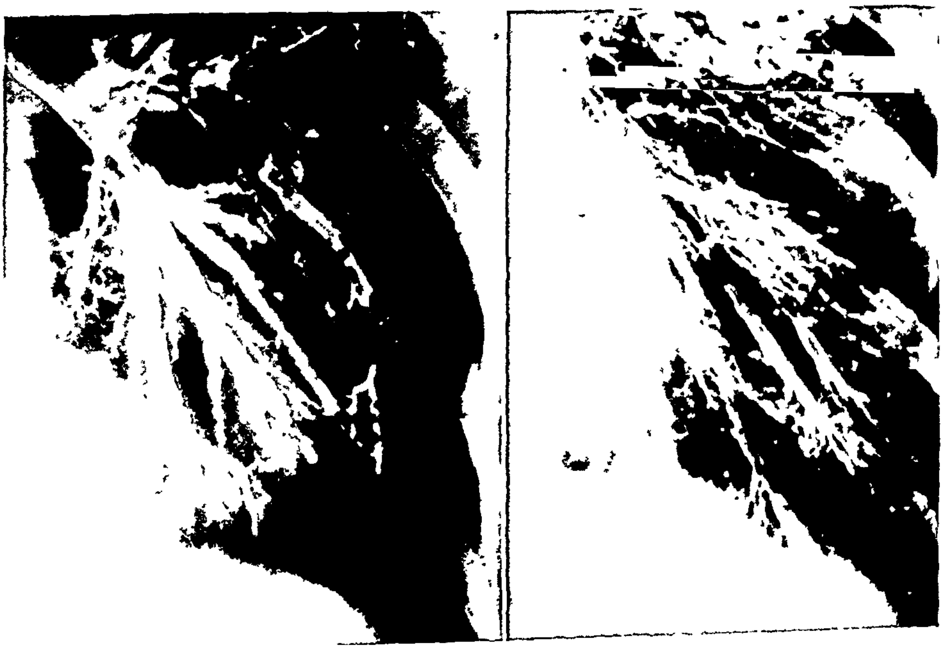

FIGURE 17A FIGURE 17B

Figure 17: Results of Conservative Treatment of Acute Bronchitis. (*A*) Changes in the bronchial outlines in the left basal segments in a patient with acute bronchitis simulate bronchiectasis. (*B*) Conservative treatment resulted in reversal of these changes as can be noted in a repeated bronchogram three weeks later.

logical appearance has been described. We believe that this study will increase our knowledge of the significance of these defects.

4. A roentgenogram made 24 hours after bronchography should become a part of the routine bronchographic procedure so that our attention can be directed to less obviously involved areas of bronchial disease. Roentgenologists should be encouraged to include this in the total cost of the bronchogram.

5. Bronchography using Visciodol has made possible a more detailed study of bronchial defects. Bronchographic findings in acute as well as various stages of chronic bronchitis are described. In order to give proper treatment to patients with acute or chronic bronchitis, these less obvious lesions must be recognized on bronchography.

RESUMEN

1. Puesto que todos los medios de contraste para broncografía producen reacción de cuerpo extraño cuando permanecen en los alveolos, se recomienda que se adopte una técnica de broncografía con un medio que no permita el llenado alveolar. Hay menos retención alveolar después de usar Visciodol que después de otros medios.

2. La técnica de la broncografía selectiva con las sondas de Metras es de valor cuando hay insuficiente delimitación de algún segmento en particular según se haya visto en broncografía previa. La broncografía de rutina en casos adecuados usando una sonda de Metras evita la necesidad de repetir los broncogramas.

3. Se describe un método para correlacionar los defectos broncográficos con su apariencia histológica. Creemos que este estudio aumentará nuestro conocimiento de la significación de estos defectos.

4. Un roentgenograma hecho 24 horas después de broncografía debe formar parte del procedimiento broncográfico de modo que nuestra atención se enfoque a las áreas menos comprometidas por la enfermedad bronquial. Los radiólogos deben animarse a incluir esto en el costo total del broncograma.

5. La broncografía con Visciodol hace posible un estudio más detallado de los defectos bronquiales. Se describen los hallazgos broncográficos en casos agudos o de bronquitis crónica. Para dar tratamiento adecuado a los enfermos con bronquitis aguda estas lesiones menos aparentes deben ser reconocidas por la broncografía.

RESUME

1. Puisque tous les produits utilisés pour la bronchographie qui stagnent dans les alvéoles peuvent se comporter comme des corps étrangers, les auteurs recommandent d'employer une technique de bronchographie et un type de produit avec lesquels on ne voie pas le remplissage alvéolaire. La rétention alvéolaire est moindre après usage de "Visciodol" qu'après tout autre produit à usage bronchographique.

2. La technique de bronchographie sélective utilisant les cathéters de Metras est de grande val eur quand le dessin d'un segment particulier s'est

montré insuffisant au cours d'un examen bronchographique préliminaire. Une bronchographie de routine, dans des cas choisis, utilisant le cathéter de Metras, évite la nécessité de bronchogrammes répétés.

3. Les auteurs décrivent une méthode qui met en parallèle les altérations bronchographiques à leur traduction histologique. Ils pensent que cette étude augmentera nos connais sances sur la signification de ces altérations.

4. Un cliché radiologique 24 heures après la bronchographie devrait faire partie de la technique bronchographique de routine, de telle sorte que l'attention puisse être dirigée sur des zones bronchiques dont l'atteinte est moins évidente. Les radiologistes devraient être encouragés à faire entrer cet examen dans le montant des frais de la bronchographie.

5. La bronchographie utilisant le visciodol a rendu possible une étude plus détaillée des altérations bronchiques. Les auteurs rapportent leurs constatations bronchographiques dans les bronchites aiguës et dans les différents stades des bronchites chroniques. Pour traiter comme il convient les malades atteints de bronchite chronique ou aiguë, il est nécessaire de reconnaitre sur la bronchographie des altérations qui apparaissent de façon moins évidente.

REFERENCES

1 Joynt, G. H. C. and Harnick, L. R.: "Bronchography with Dionosil," *Surg., Gynec. and Obst.*, 425:430, 1955.
2 Zollinger, H. U. and Fischer, F. K.: "Weitere empirische und experimentelle Untersuchungen ueber die Joduron-Bronchographie," *Schweiz. Med. Wschr.*, 25:530, 1953.
3 Storrs, R. P., McDonald, J. R. and Good, C. A.: "Lipoid Granuloma of the Lung Following Bronchography with Iodized Oil," *J. Thoracic Surg.*, *18:561, 1949.*
4 Felton, W. L.: "The Reaction of Pulmonary Tissue to Lipiodol," *J. Thoracic Surg.*, *25:530, 1953.*
5 Mackay, A., Trepanier, A. and Dufresne, M. R.: "Selective Segmental Bronchography," *American Medical Association Scientific Exhibits*, Grune and Stratton, Publisher, 1956.
6 Reid, L. McA.: "Pathology of Chronic Bronchitis," *Lancet*, 266:274, 1954.
7 Oswald, N. C.: "Chronic Bronchitis: Factors in Pathogenesis and Their Clinical Application," *Lancet*, 266:271, 1954.
8 DiRienzo, S.: *Radiologic Exploration of the Bronchus*, Charles C Thomas, Publisher, 1949.
9 Simon, G. and Galbraith, H. J. B.: "Radiology of Chronic Bronchitis," *Lancet*, 265:850, 1953.
10 Morlock, H. V. and Pinchin, A. J. S.: "Bronchial Diverticulosis," *Lancet*, 2:236, 1933.
11 Duprez, A. and Mampuys, R.: "Cystic Enlargement of the Mucous Glands of the Bronchus Associated with Chronic Bronchitis," *Thorax*, 8:141, 1953.
12 Blades, B. and Dugan, D. J.: "Pseudobronchiectasis," *J. Thoracic Surg.*, 13:40, 1943.

Bronchography: Summary of a World-Wide Survey
Report of Committee on Broncho-Esophagology

The introduction of contrast media into the bronchial tree for diagnostic purposes was first performed by Sicard and Forestier[1] in 1922. Since then bronchography has been used throughout the world and is universally recognized as a valuable aid in the diagnosis of bronchopulmonary disease. Bronchograms are made by many physicians with very different professional backgrounds: radiologists, otolaryngologists, thoracic surgeons, specialists in pulmonary disease—all are involved in the making of roentgenograms of the bronchial tree. The committee on Broncho-esophagology of the American College of Chest Physicians felt that it would be worth while to make a survey of bronchography as it is used today. We were interested in types of media, technics, anesthesia, indications and contraindications, complications and fatalities. We were interested also in the problem of bronchography in children.

With these thoughts in mind, questionnaires were prepared and sent to 60 physicians who are interested in bronchography. Twenty radiologists, 20 otolaryngologists and broncho-esophagologists and 20 thoracic surgeons were chosen. The majority of these men practice their specialty in various parts of the United States. However, several Canadians were included, eight men from Europe, two from South America and one from Japan. The results of this survey have been recorded and will be presented herein.

Findings

Replies were received from 57 of the 60 men to whom questionnaires had been sent. In some instances, the recipient of the questionnaire passed it on to one of his colleagues in related fields who usually did the work. Thus, final replies were obtained from 22 radiologists, 21 thoracic surgeons and 14 laryngologists and bronchoscopists. In some areas bronchography was a co-operative venture between a radiologist on one hand and a thoracic specialist or otolaryngologist on the other. This was very often true in children in whom anesthesia was required, and the contrast medium was instilled through a bronchoscope or an endotracheal tube. If both bronchoscopy and bronchography were indicated, 25 specialists indicated that they performed both procedures on the same day with the same anesthesia, while 28 others almost always made a separate procedure of bronchography.

In preparation for bronchography, postural drainage was employed by more than half of the participants but was almost routine after the procedure. Aerosol bronchodilators were administered just before bronchography at times, and occasionally aerosol detergent preparations were used. Sedative medications of the barbiturate type were given to patients by 41 men, and 25 used atropine routinely for premedication. The use of opiate derivatives such as morphine, codeine, demerol and even heroin was advocated by 35 of the participants but was sharply criticized by many men. Nine thoracic surgeons gave drugs of the antihistaminic group prior to instillation of the contrast medium. Premedication was not used by 12 men who responded to the questionnaire.

Local anesthesia was employed universally among adults. Cocaine and pontocaine were the favorite agents but several of the correspondents favored cyclaine, xylocaine or other surface anesthetics. Occasionally Forrester's solution, commonly used for bronchospirometry, was recommended (Table I). These agents not only were applied topically to the hypopharynx by many but also were instilled into the trachea and bronchi with the aid of a Luken's type syringe. All agreed that proper anesthesia was essential for good bronchograms.

The technic of instilling the contrast medium varied greatly, but the great majority of men expressed a preference for the catheter method. Nearly always, a No. 14 catheter was passed through one of the nostrils and then guided into the trachea. Ten of the 57 specialists still prefer supraglottic instillation, and one surgeon instills the medium into the hypopharynx through a nasal catheter. The transtracheal technic is employed by only three of our correspondents. Although this method has enjoyed considerable favor in Great Britain, it has been virtually abandoned by specialists in the United States because of the occasional complication that follows insertion of the needle through the tracheal wall.

The choice of contrast media was of special interest (Table II). Many of the men used one agent exclusively and were most emphatic in their preference. However, others used two or more preparations, and it was evident that they are still searching for the ideal substance for bronchography. A small but determined group of investigators employed an iodized oil thickened with sulfanilamide. They pointed out that alveolar filling is rare with thick Lipiodol but they do admit that the procedure is very time consuming. Oily Dionosil (propyliodone) is certainly the favorite preparation at the present time. The enthusiasm for aqueous dionosil seems to be waning, partly because the material is irritating and partly because of unfavorable reactions and even fatalities. In dionosil the iodine is in organic combination and there is no risk of iodism. Propyliodone (Cilag) is very similar to dionosil and appears to be a satisfactory medium, according to Swiss authorities. Umbradil viscous B is rarely used.

TABLE I

LOCAL ANESTHETIC AGENT USED FOR BRONCHOGRAPHY (57 REPLIES)*

Drug	Participants, Number
Tetracaine hydrochloride (pontocaine)	31
Cocaine	28
Lidocaine hydrochloride (xylocaine)	8
Hexylcaine hydrochloride (cyclaine)	7
Forrester's solution	2
Others	4

*Several participants listed two or more agents.

TABLE II

CONTRAST MEDIA USED FOR BRONCHOGRAPHY (57 REPLIES)*

Medium	Participants, Number
Oily dionosil	29
Aqueous dionosil	18
Lipiodol	15
Iodochloral	14
Lipiodol with sulfanilamide	3
Propyliodone (cilag)	1
Umbradil	1
Maljodal (Japanese)	1

*Several participants used two or more media.

The quantities of media used for bilateral bronchograms varied greatly. Forty-nine of the participants provided satisfactory replies to this question (Table III). It seemed obvious that a larger quantity was needed when oily Dionosil was used, but the larger amount was apparently well tolerated.

Only seven of the 57 participants stated that complete bronchography was not routine. Forty-four made bilateral bronchograms on the same day with the same anesthesia, while 13 specified that each side of the bronchial tree was filled separately on different days. Of the 50 physicians who answered the question regarding fluoroscopy 34 instilled the contrast medium with fluoroscopic guidance, while 16 did not use the fluoroscope.

The majority of bronchographers instilled media into the right side of the bronchial tree first and obtained films made in the anteroposterior, right posterior oblique and right lateral projections (Table IV). Then, either immediately or at a subsequent session, the left side was filled and anteroposterior and left posterior oblique views were made. A few men filled both sides of the bronchial tree before taking films and were content with anteroposterior and both oblique projections. In the majority of instances, four to six films (14 by 17 inches) were employed. Very few made stereoscopic films.

Spot films were used routinely by 12 correspondents, while others made spot films occasionally. The Metras catheters with the curved tip are particularly useful for selective bronchography. These were used to good

TABLE III

MEDIA FOR BILATERAL BRONCHOGRAPHY (49 REPLIES)*

Amount of Contrast Media, Cubic Centimeters	Participants, Number
Less than 20	4
20 to 25	13
30 (about)	17
40 (about)	15

*Eight participants did not answer this question.

TABLE IV
DATA ON ROENTGENOGRAPHY (57 REPLIES)

View	Number of Films	Number Who Used
Posteroanterior and both obliques	3	2
Posteroanterior, right lateral, both obliques	4 to 8	43
Posteroanterior, right lateral, both obliques, plus spot films	8 or more	12

advantage by several European and Canadian bronchographers. The majority, however, relied on various posturing technics in order to map out the various segments of the lung. The x-ray tilt table was rather useful for placing the patient in a variety of positions during and after instillation of medium. Most men agreed that accurate timing was desirable for optimal filling of the bronchial tree, while others relied on fluoroscopic control. Individual technics varied tremendously, and yet it was obvious that all of the correspondents were capable of obtaining satisfactory bronchograms.

All physicians who replied agreed that the demonstration and localization of bronchiectasis were by far the most important indication for lung mapping (Table V). There was considerable difference of opinion about the value of bronchograms in the diagnosis of bronchial tumors; the radiologists were rather enthusiastic about the method, while many of the broncho-esophagologists and surgeons felt that bronchograms were neither necessary nor desirable. A similar disagreement was evident regarding the value of bronchograms in tuberculosis. Many felt that radiopaque material should be instilled only if there was a strong clinical suggestion that bronchial disease accompanied tuberculosis. It was interesting to note that bronchography was seldom employed for the diagnosis of lung abscess but it was used very often in the evaluation of hemoptysis

TABLE V
USE OF BRONCHOGRAPHY: INDICATIONS AND CONTRAINDICATIONS (57 REPLIES)

Condition Indicating Use	Participants Who Agreed	Condition Contra-indicating Use	Participants Who Agreed
Bronchiectasis	57	Iodine-sensitivity (history)	30
Indeterminate hemoptysis	50	Recent pneumonitis	26
Bronchostenosis	43	Heart disease	18
Bronchial tumors	38	Asthma	18
"Middle-lobe syndrome"	36	Emphysema	16
Chronic cough	23	Trauma (acute)	14
Tuberculosis	17	Tuberculosis (active)	12
Abscess of lung	4	Advancing age	11

sis of obscure origin. It was not used too frequently for the study of chronic coughs.

The principal contraindications to bronchography are listed in Table V. The committee was surprised that a greater number of physicians did not fear the introduction of opaque material in patients having diseases such as asthma, emphysema and heart disease, and in older people. A few who answered still feel that bronchography is hazardous in pulmonary tuberculosis, and a number of instances were cited in which dissemination of tuberculosis had resulted. Many feel that the risk of iodine sensitivity is greatly reduced if dionosil is used instead of iodized oil.

All participants described some complications but considered them rare (Table VI). Some of the untoward effects could be attributed to obstruction of the bronchi by the contrast material. Others were thought to be manifestations of iodine sensitivity. Four men use a skin test to check for iodine sensitivity, while two others give iodine orally for the same reason. All agreed that iodized oil in the stomach was the principal source of iodine reaction. Three men routinely lavaged the stomach, while one authority gave a cornstarch preparation following bronchography to absorb the iodine. Granuloma of the lung in resected specimens was described by 10 of our correspondents. It was noted after oily preparations were used but less frequently with aqueous preparations having a carboxymethyl cellulose base. The granulomatous reaction occurred especially after massive bronchial and alveolar filling. Several authorities still recommend that pulmonary resection be deferred for 3 to 4 weeks after a bronchogram has been made.

Seventeen fatalities were reported in connection with the making of bronchograms. Eight of these occurred after administration of local anesthetics but before any contrast medium was instilled. In the other nine, however, death occurred after the contrast substance was introduced

TABLE VI
COMPLICATIONS OF BRONCHOGRAPHY (57 REPLIES)* †

Complication	Number Who Had Encountered
Fever	29
Skin lesions	22
Facial edema	19
Asthma	19
Pneumonitis	16
Parotitis	15
Granuloma (removed specimens)	10
Pneumothorax	5
Dissemination of tuberculosis	4
Atelectasis	3

*Reactions to local anesthesia excluded.
†Incidence of complications estimated from 0.5 to 2 per cent.

(Table VII). It is estimated that the combined experience of our 57 collaborators probably represents a total of some 50,000 to 100,000 bronchograms. Hence, the mortality rate is very low, but bronchography is not without risk.

Part of our questionnaire was devoted to the problems of bronchography in children. Forty-eight of the 57 men reported experience with children (Table VIII). In small children general anesthesia was almost universally employed. A few authorities felt that satisfactory bronchograms could be obtained with local anesthesia or even no anesthesia. Ether was the agent of choice and was considered safest. Eleven men used pentothal

TABLE VII
DATA CONCERNING NINE FATALITIES OWING TO BRONCHOGRAPHY*

Case	Age Group	Contrast Medium	Cause of Death
1	Child	Aqueous dionosil	Anoxia; cystic lung disease
2	Child	Lipiodol	Anoxia; mucoviscidosis
3	Adult	Oily dionosil	Anoxia; bronchospasm
4	Adult	Oily dionosil	Anoxia; emphysema (excess sedation)
5	Adult	Aqueous dionosil	Anoxia; emphysema
6	Adult	Oily dionosil	Anoxia; bronchospasm (bronchiogenic cancer)
7	Adult	Lipiodol	Iodine sensitivity, with bullous skin lesions
8	Adult	Iodochloral	Dissemination of tuberculosis
9	Adult	Oily dionosil	*Cardiac arrest*

*Combined experience of all 57 physicians who replied.

TABLE VIII
BRONCHOGRAPHY IN CHILDREN (48 REPLIES)*

Anesthesia: Type, Agent, Route	Participants, Number
Anesthesia:	
Local	8
Local with tribromoethanol (avertin) given rectally	3
Ether	34
Thiopental sodium (pentothal) given intravenously	11
Nitrous oxide	1
Method or route of introduction:	
Bronchoscope	11
Catheter	31
Endotracheal tube	6
Transglottic	2

*Some men did not do bronchography in children; others used more than one method.

sodium intravenously and most of these used a technic employing both an intratracheal tube and a catheter. Avertin, given rectally, and nitrous oxide were used rarely. The medium was instilled via a catheter by 31 men, via the bronchoscope by 11, through an endotracheal tube by six, and by injection through the anterior wall of the trachea by two participants. The same types of media were used for children, but about half of the quantity used for adults was instilled. Indications for bronchography are much the same in children and adults, but the method can be used for the diagnosis of cystic disease of the lung, tracheo-esophageal fistula, congenital anomalies and also for the pulmonary manifestations of fibrocystic disease of the pancreas.

Contraindications to bronchography in children are similar to those in adults. However, certain hazards in the performance of bronchography in infants and children must be borne in mind. In addition to the risks of general anesthesia, the possibility of laryngeal edema also must be considered. Furthermore, the presence of large amounts of contrast media in the bronchial tree may produce asphyxia and in some instances has been responsible for death.

In general, the majority of men were of the opinion that bronchography in children was reliable. However, 12 of them felt that interpretation of the bronchograms in children was difficult and that it often was not easy to interpret the extent of the disease. Some of the thoracic surgeons were particularly concerned about the reliability of bronchography in children.

All of the participants were asked whether bronchography was being employed to a greater or lesser extent in their practice. About two thirds of those who answered the question felt that bronchography was being used with increased frequency. Although less bronchiectasis was encountered, the procedure was used oftener for investigation of hemoptysis, bronchostenosis and chronic cough than for bronchial tumors and tuberculosis. In evaluation of bronchial obstruction and cavitation, tomography is replacing bronchography as a radiographic technic.

Comment

The Committee on Broncho-esophagology realizes that the participants in this questionnaire were a selected group and that, therefore, the opinions expressed may not be representative. Nevertheless, many of the men who were contacted are considered authorities on bronchography and many of them have published articles on this method of examination. As previously stated, it has been estimated that the combined experience of the group would probably total between 50,000 and 100,000 bronchographic examinations. The committee is very grateful to the participants for the fine cooperation shown in this project. In addition to completing the questionnaire, a number of the men wrote lengthy letters with discussions of various points, and a number sent reprints which reflected their experience.

CONCLUSIONS

The participants in this study and the members of the Committee on Broncho-esophagology consider bronchography to be an important diagnostic aid. Bronchography should be done by physicians with training and experience who are willing to take the time to do it well. It should not be delegated to the inexperienced intern or resident. Too often bronchography is treated as a "stepchild." If bronchography is worth doing at all, it should be done well.

No longer do we think of bronchography as merely a means of confirming a diagnosis of bronchiectasis already suspected or as a roentgenoscopic demonstration of an obstruction already seen through the bronchoscope. Today the thoracic surgeon requests precise information as to the segments involved in bronchiectasis of tuberculosis, and above all he wants to know which bronchi are normal. In segmental resection of the lung the results may be disastrous if this information is not available to the surgeon. Thus complete bilateral bronchography is essential.

Even the most experienced bronchographer does not claim more than 90 per cent success in obtaining adequate bronchograms, and in less capable hands the number of poor bronchograms is considerable. Hence, it is obvious that there is plenty of room for improvement in the technic of bronchography. Good anesthesia is essential but the agent must be administered within the limits of safety. We are still searching for the perfect contrast medium and present technics can certainly be improved. Bronchography in children deserves particular attention, both with respect to selection of patients and to performance of the procedure. Of prime importance is the maintenance of an airway for the administration of oxygen. At present it would seem that both an intratracheal tube and a catheter should be passed into the trachea so that oxygen can be given before, during and after the instillation of the contrast substance.

Interpretation of bronchograms requires a thorough knowledge of bronchial anatomy and the common bronchial variations. Considerable experience is essential for the reading of bronchograms, and interpretation should be correlated with the clinical problem as well as other roentgenographic studies of the thorax. Bronchospasm, retained secretions and recent pneumonitis or atelectasis may profoundly alter the bronchographic pattern. Too often an opinion is expressed on an inadequate bronchogram.

Much remains to be learned about the physiology of the bronchial tree. A good deal of information can be obtained by motion pictures of the fluoroscopic image of the bronchial tree filled with contrast medium. Up to the time of this report such technics have been impractical because of the radiation hazard. It is hoped that with improvements in image-amplifier equipment, the bronchial tree can be studied in action. Hence, it is possible that bronchography will make a contribution to our knowledge of pulmonary physiology as it already has to bronchial anatomy.

Committee on Broncho-esophagology

Arthur M. Olsen	*Chairman*, Rochester, Minnesota
Paul C. Samson	Oakland, California
George S. McReynolds	Galveston, Texas
Arthur J. Cracovaner	New York, New York
Everett C. Drash	Charlottesville, Virginia
Paul H. Holinger	Chicago, Illinois
Chevalier L. Jackson	Philadelphia, Pennsylvania
Earle B. Kay	Cleveland, Ohio
Andre MacKay	Montreal, Quebec
C. Benjamin Schoemperlen	Winnipeg, Manitoba

REFERENCE

1 Sicard, J. A. and Forestier, J.: "Méthode générale d'exploration radiologique par l'huile iodée (Lipiodol)," *Bull. et mém. Soc. méd. hôp. Paris*, 1:463, 1922.

Discussion

SHELDON E. DOMM, M.D., F.C.C.P.
Knoxville, Tennessee

Of the many points raised by these two excellent papers there should be no question regarding one statement from the first presentation, "All of the men who participated in this questionnaire agree that bronchography is an important diagnostic aid and that it certainly should not be treated as a stepchild." It is refreshing to hear this after reading a recent paper from which one gets the impression that at one institution bronchograms apparently are made and interpreted by the junior residents.

The Committee on Bronchoesophagology of the College is to be commended for making this timely survey of bronchography. And the Program Committee deserves credit for including this subject on the program, and for selecting Dr. Rayl and Dr. Smith to give the findings of the extensive and dedicated studies they and their associates are making at Oteen.

I am sure all of us in this room who are doing bronchography could take issue with many of the details presented by the two essayists. It is well, however, to repeat the wise observation of Dr. Olsen that "individual techniques vary tremendously, yet it is obvious that all the correspondents are capable of obtaining satisfactory bronchograms."

In this connection it might be mentioned that there is a tendency toward oversimplification inherent in the questionnaire approach. This is shown by the fact that a number of the men wrote lengthy letters in addition to completing the questionnaire, and also by the fact that in many of the categories some men listed more than one technique or material.

Nevertheless a sufficient number of controversial points remain to provide heated argument on every one of the 18 questions. For example only

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half of the participants use postural drainage in preparation for bronchography. This should be routine. The questionnaire did not make clear how many men believe in doing diagnostic (and possibly therapeutic) bronchoscopy some days or weeks prior to bronchography. We believe this should be routine with few exceptions.

I was interested to see that the majority fill the right side first, presumably regardless of the location of the lesion. This habit seems no more logical than the practice of one man I know who always fills the left side first simply because it is harder to fill. We believe the more involved side should be mapped first so that a true lateral film, certainly the most valuable view for the surgeon, can be obtained.

The alleged disagreement regarding the value of bronchography in tuberculosis may simply reflect Dr. Olsen's observation that "our correspondents are not working much with T.B." It is my understanding that preoperative bronchography is routine in most tuberculosis centers at the present time, and my opinion that it should be.

I was glad to see waning enthusiasm for aqueous Dionosil, and equally glad to note that Oily Dionosil is the favorite preparation at this time. In this connection Dr. Rayl's experiment showing retention of the peanut oil in spite of the disappearance of the radiopaque propyliodone is of great interest from the pathological point of view. The experience of most men, however, seems to be that Dionosil Oily does not foul up one's subsequent x-ray series by virtue of alveolar retention insofar as x-ray interpretation is concerned. This is the crux of the Dionosil-Visciodol controversy. One notes that Dr. Rayl reports an 18 per cent reduction in the per cent of objectionable alveolar retention following Visciodol instillation, by the use of Vaponephrin bronchodilatation. This gives a figure of 6 per cent retention as compared to an earlier estimate of 15 per cent (without Vaponephrin). These figures, reflecting our experience, seem unacceptably high. We would not use Visciodol in a case in which alveolar retention of radiopaque medium must be avoided.

Dr. Rayl and Dr. Smith have made a nice contribution in the development of a technique of injecting surgical specimens with an opaque medium which solidifies. They should be commended also for stressing the importance of bronchitis in any consideration of bronchography and bronchiectasis; this is a most neglected and most important subject. We also believe in the value of a routine x-ray film a day or two following bronchography, having made some interesting diagnoses by this simple device.

Not knowing whether Dr. Henry Houghton of South Africa had been polled by Dr. Olsen I wrote to Dr. Houghton who, as you know, reported in 1953 a series of 7,000 bronchograms using Lipiodol thickened with Sulfanilamide, inquiring whether he is still enthusiastic regarding its use. Dr. Rayl will be encouraged to know that the "small but determined group" of Visciodol advocates referred to by Dr. Olsen still has a champion in Dr. Houghton who is "well satisfied with Visciodol."

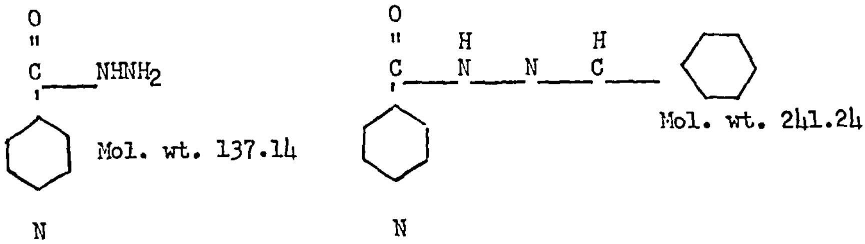
Sheldon E. Domm, M.D.

A Preliminary Report on the Safety and Therapeutic Activity of a Salizid INH Derivative

W. E. ROYE, M.D., F.C.C.P. and G. E. EWART, M.D.
Richmond, Virginia

Although the development of INH greatly advanced the chemotherapy of pulmonary tuberculosis, there are many cases that still cannot be controlled adequately. As a consequence there is a continued search for agents which might provide greater inhibition of the tubercle bacillus with even less toxicity for man. Among the newer of the hydrazine derivatives is salicylidene hydrazine (Salizid® Nepera). This report covers our preliminary investigation of the toxicity, and the therapeutic activity of this compound.

Salizid is obtained from the interaction of the isonicotinic acid hydrazide and salicylaldehyde. It is sparingly soluble in the ordinary solvents and does not lose its inhibitory activity against *myobacterium* upon autoclaving for two hours at 20 pounds pressure. The difference in chemical structure between INH and Salazid is shown in Figure 1.



INH

Salizid

FIGURE 1

Hart[1] et al first reported that Salizid was strongly inhibitory against $H_{37}R_v$ *in vitro*. Resistant $H_{37}R_v$ cultures were found to die out in a few passages and organisms resistant to several other antituberculosis compounds were found, *in vitro,* to be sensitive to this compound. Steenken[2] et al, however, found that Salizid retained only a slight degree of inhibitory activity against the resistant $H_{37}R_v$ strain. This *in vitro* finding was substantiated by animal studies as only a few of the guinea pigs inoculated with INH resistant strain responded better to Salizid than to INH and other INH derivatives. Both of these authors suggested that Salizid merited thorough clinical study, particularly in INH sensitive disease.

In early clinical trials, McCormick[3] et al reported that Salizid was well tolerated in large doses and that a majority of the patients who develop peripheral neuritis as a result of INH therapy may be treated safely with this agent. The response in 50 original treatment patients was prompt and excellent in 41, delayed, but good in four, symptomatic improvement

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From the Medical Service, Veterans Administration Hospital.

TABLE I
E.E.G.

	Dec.	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	
P. W.	N 0 mgm			N 400 mgm		N 800 mgm			N 1200 mgm			
J. Y.			M. A. 0 mgm	0					? 800 mgm		N 800 mgm	Improvement on serial study
S. R.	M. A. 0 mgm			M. A. 400 mgm							M. A. 800 mgm	No change on serial study
E. H.	N 0 mgm			N 400 mgm		N 800 mgm			Surgery dropped from study			
J. E.	N 0 mgm		Too weak for further testing									
M. G.		M. A. 0 mgm		M. A. 400 mgm		M. A. 800 mgm			N 1200 mgm		M. A. 1200 mgm	No change on serial study
A. S.	N 0 mgm			N 400 mgm		N 1200 mgm			N 1200 mgm		N 1200 mgm	No change on serial study

N—Normal

M. A.—Mildly and moderately abnormal

"mgm" refers to mgm. of Salizid per day at the time of the E.E.G.

with only slight roentgenographic improvement in two, and three deaths. Ewart and Wingo[4] also reported that this compound was safe in doses of at least 1200 mgm. per day. These investigators found that INH resistant cases at 300 mgm. per day were not benefited by larger doses of Salizid. Recently, Nagley[5] reported that Salizid was an excellent and safe agent for the treatment of pulmonary tuberculosis and that in human beings, resistance was not built up as quickly to Salizid as to INH.

In our preliminary investigations, in 18 tuberculous men we attempted to determine the toxicity of this compound and its therapeutic value in: a) cases of peripheralneuritis, b) SM-PAS failures, c) seriously ill cases of pulmonary tuberculosis, d) INH resistant cases.

1) *Toxicity Evaluation.*—This part of our evaluation was carried out in seven colored men 25 to 65 years of age. All of these had a history of multiple admissions for chronic, far advanced active pulmonary tuberculosis. All had failed to respond to SM-PAS therapy, and had shown all clinical and laboratory evidence of being resistant to INH. Salizid was given for a minimal period of eight months and a maximum of 22 months.

The average dosage received by this group is summarized as follows:

4 months on 400 mgms. a day
5 months on 800 mgms. a day
6 months on 1200 mgms. a day

and in addition two other patients received 1600 mgm. daily for 10 months.

All were studied for possible neurotoxicity and hepatoxicity:

a) Neurotoxicity—there was no objective evidence of neurotoxicity. There was no euphoria or nervousness. In all, 23 electroencephalograms were carried out on six patients, and no abnormality was initiated or aggravated in any. The data for an 11 month period during the study is shown in Table I. Serial study gave the impression that there was a serial slowing of the pattern. This slowing was greater than one could expect from six unselected patients; but nevertheless was not enough of a slowing to be considered abnormal in any one of the cases studied.

b) Liver toxicity—no case was discontinued and no dosage reduced because of toxicity. A battery of liver function tests were performed at two week intervals during the first two months. After the second month, the tests were reduced to monthly determinations of serum bilirubin, thymol turbidity, cephalin flocculation and B.S.P. retention. Thymol turbidity, cephalin flocculation, cholesterol, prothrombin time, alkaline phosphatase and cholesterol esters, produced a number of minor variations similar to previous values on these and similar patients on INH therapy. Direct, indirect and total serum bilirubin demonstrated no abnormality on approximately 200 determinations.

The bromsulfalein excretion tests were more difficult to interpret. The three most severely ill patients had a scattering of B. S. P. retention values ranging from 10 to 25 per cent. They demonstrated no consistent pattern. There was no liver damage demonstrated when they were examined at post-mortem and the mode of death did not suggest liver toxicity.

The individual cases are summarized in Table II. Only one case (A. S.)

TABLE II

SUMMARY OF TOXICITY STUDY

Patients Name	400 mg.	800 mg.	1200 mg.	1600 mg.	Final Disposition	Change	Function Liver Findings	E. E. G.	P. M. Findings
J. E.	3 mo.	8 mo.	1 mo.		Death—Heart failure	Not evaluated because of edema	Normal	Not done too weak	Liver normal
M. G.	10	3	5	4 mo.	Death—Advanced Tbc.	—8 pounds possible due to edema	Normal	No change, on serial study	Liver normal
S. R.	3	8	10		Lobectomy	—4 pounds	Normal	No change, on serial study	
A. S.	3	3	7		Death—Advanced Tbc. & empyema	—10 pounds progressive empyema	Serial BSP, abnormal	No change, on serial study	Liver normal
P. W.	3	3	5	10	No change in Tbc. at end of study	No change	Normal	No change, on serial study	
J. Y.	3	5	6		No change	No change	Normal	Improvement on serial study	
E. H.	4	4			No change	+5 pounds	Normal	Dropped from study	

showed any abnormal change in liver function (B. S. P.) during the entire study which might have indicated possible liver damage. On postmortem examination the liver showed no evidence of toxic changes.

Effect in Cases with Peripheral Neuritis

Salizid was administered to a total of seven tuberculous patients, whom we desired to treat with INH, but who had various neurological disorders. The dosage of Salizid for these cases was 300 mgm. a day, a dosage equivalent to the routine dose of INH. The neurologic conditions were a result of either alcoholism, post-gastrectomy syndrome, nutritional deficiency, or diabetes.

Four of these cases were in on their first admission for treatment of tuberculosis. Clinically, they all did well in regard to both the pulmonary tuberculosis as well as the neurologic symptoms. All were dismissed from the hospital, after six months or more of therapy, three being classified as having inactive tuberculosis and the fourth was discharged with apparently negative sputum but an open healing cavity.

One hospitalized chronic patient receiving INH developed peripheral neuritis which cleared when placed on Salizid therapy. This case was complicated by a nutritional deficiency, so that we could not be entirely certain that the neuritis was completely a result of INH. However, whatever the cause, it cleared during treatment. The sixth case had neurologic symptoms due to a spinal cord compression. The severity of symptoms was reduced during Salizid administration, however, the chronic, minimal tuberculous focus in this patient has been unchanged.

The last case in this group presented a diagnostic chest problem. In addition he had a chronic, progressive neurologic disease, which made INH therapy precarious. However, following one year of Salizid, he was released from the hospital with a negative sputum and no aggravation of the neurologic condition either during or following the period of Salizid therapy.

SM-PAS Failure

A man with a persistent open cavity, positive sputum and laboratory studies indicative of resistance to both streptomycin and PAS was on his initial treatment with INH. Salizid 100 mgm. t.i.d. was added to his SM-PAS therapy. Eleven months later, he was discharged with a diagnosis of inactive tuberculosis.

Seriously Ill Admissions

One of the cases in this group, a first admission, required, because of severity of lesions, what can be considered as heroic treatment. Salizid 800 mgm. a day with pyrazinamide 3 gm. a day was selected. The hospital course thereafter was uneventful. Examination of the lobe resected 11 months later revealed only a 1 cm. epitheloid cavity and no soft caseous nodule. The PZA was stopped after 14 months. He remains on Salizid 800 mgm. a day with no evidence of adverse effects.

One of the cases listed under peripheral neuritis can be included also in this group of desperately ill patients. In addition to having far advanced pulmonary tuberculosis and severe nutritional deficiency, he presented tuberculous peritonitis and a history of alcoholism and chronic liver disease. There was evidence of abnormal liver function. Running a stormy, febrile course with alternating brief remissions and exacerbations, he received in a three month period, varying combinations of streptomycin, INH, PZA, tetracycline and oxytetracycline; and death seemed imminent. Following these various therapies, and as a last resort, he was placed on Salizid 300 mgm. a day and streptomycin 1 gm. twice a week. The clinical course was uneventful. It is difficult in retrospect to separate the findings of severe disease from those of drug reactions during the first three months, however, the clinical improvement upon shifting to the SM-Salizid in this case was definite.

INH Resistant Cases

Included in this group of INH resistant cases receiving Salizid are the seven cases from the toxicity study, one of the neurologic cases, and an additional case resistant to INH. Large doses up to 1600 mgm. were given. In some instances the clinical impression was that the advance of the tuberculous lesion was slower than it would have been had the patient gone untreated. However, the effect of Salizid in these INH resistant cases was not impressive enough to encourage us to continue Salizid therapy indefinitely. In another instance we employed Salizid, 800 mg., in a patient whose tuberculosis was rapidly increasing in severity. These lesions appeared to be arrested, but we could not attribute the therapeutic benefit obtained entirely to the Salizid, as other chemotherapeutic agents had been administered concomitantly. However, in spite of clinical improvement the cavity has not closed after five months of therapy.

SUMMARY

Salizid, the salicylaldehyde salt of INH, was tried in a series of 18 cases. In a toxicity evaluation doses up to 1600 mg. daily were employed for as long as 10 months. No evidence of neurotoxicity or hepatic damage was obtained from EEG tracings, liver functions tests, or post-mortem examinations. In addition, it is well tolerated in doses of 300 mgm. daily by patients having neurologic disease even with peripheral neuritis resulting from INH. Cases resistant to INH do not respond to larger doses of Salizid. When given in combination with other chemotherapeutic agents, in advanced pulmonary tuberculosis it may be of some benefit. Salizid is an excellent drug and merits further usage in pulmonary tuberculosis because of its safety and chemotherapeutic action in cases of INH sensitive tubercle bacilli.

RESUMEN

El Salizid, que es el salicilaldehido de INH, se ensayó en un grupo de 18 casos. Al valuar su toxicidad se usaron dosis hasta de 1.600 mgr. diarios hasta por diez meses. No se encontró evidencia de neurotoxicidad o de daño hepático según los ECG, las pruebas de función hepática o los exámenes postmortem. Además, es bien tolerado a la dosis de 300 mgr. diarios por enfermos con afecciones neurológicas y aún con neuritis periférica consecutiva a la INH.

Los casos resistentes a la INH no responden a dosis más grandes de

Salizid. Cuando se da combinado con otros agentes quimioterápicos en tuberculosis pulmonar avanzada, puede ser de alguna utilidad.

El Salizid es una droga excelente y merece que se le use más en tuberculosis pulmonar por su seguridad y su acción quimioterápica en casos de bacilo tuberculoso sensible a la INH.

RESUME

Le "salizide," sel salicylaldehyde de l'isoniazide, a été essayé sur un groupe de 18 malades. Pour évaluer la toxicité de ce produit, des doses allant jusqu'à 1600 mmgr. par jour furent utilisées pendant une durée atteignant dix mois. On n'obtint aucune preuve de neurotoxicité ou d'atteinte hépatique d'après les tracés encéphalographiques, les tests de la fonction hépatique, et les examens post-mortem. De plus, il fut bien toléré aux doses de 300 mmgr. par jour chez des malades ayant des affections neurologiques, avec atteinte périphérique résultant de l'isoniazide. Les cas résistants à l'isoniazide ne sont pas influencés par des doses plus importantes de "salizide." Lorsque ce produit est donné en association avec d'autres agents chimiothérapiques, dans les cas de tuberculose grave, il peut avoir quelque action favorable. Le salizide est une excellente médication et mérite un emploi plus étendu en tuberculose pulmonaire, à cause de son innocuité et de son action chimiothérapique dans les cas de bacilles tuberculeux sensibles à l'isoniazide.

ZUSAMMENFASSUNG

Salizid, das Salicylaldehyd-Salz von INH, wurde erprobt in einer Reihe von 18 Fällen. Zur Auswertung der Toxicität wurden Dosen bis 1600 mg. täglich angewandt für eine Zeit von 10 Monaten. Es ergab sich kein Anhalt für Neurotoxicität oder Leberschädigung, wie aus den EEG-Aufzeichnungen, Leberfunktionsprüfungen oder Sektionsbefunden hervorgeht. Ausserdem wird es gut vertragen in Mengen von 300 mg. täglich auch von Kranken mit neurologischen Erkrankungen, sogar mit peripherer Neuritis infolge INH. Gegen INH resistente Fälle reagieren nicht auf grössere Dosen von Salizid. Wird es bei fortgeschrittener Lungentuberkulose in Kombination mit anderen chemotherape-utischen Stoffen gegeben, so kann es von einigem Nutzen sein. Salizid ist ein ausgezeichnetes Mittel und verdient weitere Verwendung bei Lungentuberkulose wegen seiner Harmlosigkeit und chemotherapeutischen Wirkung in Fällen von INH-sensibilen Tuberkelbazillen.

REFERENCES

1 Hart, J. J. D., Rutherford, S., Anderson, F. E., Barkley, F. A. and Mast, G. W.: "In Vitro Activity of N-isonicotimoyl-N'-(salicydene) Hydrazine (Salizid) Against Mycobacterium Tuberculosis," *Antibiotics and Chemotherapy*, 4:803, 1954.

2 Steenken, W., Jr., Wolinsky, E. and Montalbine, V.: "Effect of Two Isoniazid Derivatives and PAS Hydrazide on Isoniazid Susceptible and Resistant Tubercle Bacilli (21348) ," *Proc. Soc. Exper. Biol. and Med.*, 87:245, 1954.

3 McCormick, G., Katz, S., Gimble, A., Leonard, J., Schmidt, W. and Shea, J.: "The Use of Large Doses of Salizid in Pulmonary Tuberculosis: Transactions of the 14th Conference on the Chemotherapy of Tuberculosis," *V. A., Army, Navy*, 331, 1955.

4 Ewart, G. E. and Wingo, C.: "Salizid, A Study of Hepatic and Neurotoxicity: Transactions of the 14th Conference on the Chemotherapy of Tuberculosis," *V. A., Army, Navy*, 331, 1955.

5 Nagley, N.: *Presented at the Meeting of the American College of Chest Physicians in Chicago*, June, 1956.

Bilateral Middle Lobe Syndrome

WATTS R. WEBB, M.D., F.C.C.P.
Jackson, Mississippi

Since its first use by Graham, Burford and Mayer,[1] the "middle lobe syndrome" has become well accepted both as a clinical syndrome and as a concept of pathogenesis. Any inflammatory process of the right lung may cause enlargement of the collar of lymph nodes around the long slender middle lobe bronchus with obstruction and distal pneumonitis. This increases the lymphoid tissue response and the obstruction persists with the formation of a vicious cycle, often broken only by surgery, though acute reversible forms may occur.[2] It is also well accepted that an analogous process may involve lobes or segments other than the right middle lobe.

Packard,[3] in 1928, first reported that tuberculous lymph nodes may cause sufficient extrinsic pressure to produce complete bronchial obstruction and massive collapse of the lung even in adults. In 1946, Zdansky[4] and Brock[5] independently pointed out the significance of right middle lobe atelectasis. Zdansky noted that, in children, total lobar atelectasis will frequently be caused by lymph node compression of the bronchi without predilection for any one lobe or bronchus as all bronchi are quite small. In adults, however, atelectasis of an entire lobe occurs with frequency only in the right middle lobe where the bronchus is long, narrow and rendered even more vulnerable by the right angle it forms with the intermediate stem bronchus. In other lobes, segmental bronchial compression with segmental atelectasis is the rule.

Brock, in "The Anatomy of the Bronchial Tree,"[5] also noted the frequency of right middle lobe obstructive pneumonitis. He demonstrated that the right middle lobe bronchus is in the lymphatic drainage pathway of both the right middle and right lower lobes, thereby making it vulnerable from respiratory infections of either lobe. He also mentions the vulnerability of the left upper and lower lobes whose bronchi are surrounded by many nodes at their origin.

As the lingula represents the homolog of the right middle lobe, it has often been referred to as the "left middle lobe." The lingular bronchus is similar to the right middle lobe bronchus in that it is rather long, narrow and bifurcates into two long, narrow divisions. It likewise has a significant cuff of surrounding nodes, but differs in arising from its parent bronchus at a less acute angle which is conducive to better drainage. While the lingula is frequently involved in nontuberculous bronchiectasis, it is less commonly the site of obstructive pneumonitis. In the following two cases, bilateral resections were performed for simultaneous involvement of the right middle lobe and of the lingula with obstructive pneumonitis. This has not been recorded previously.

From the Mississippi State Sanatorium and the Department of Surgery, University of Mississippi School of Medicine.

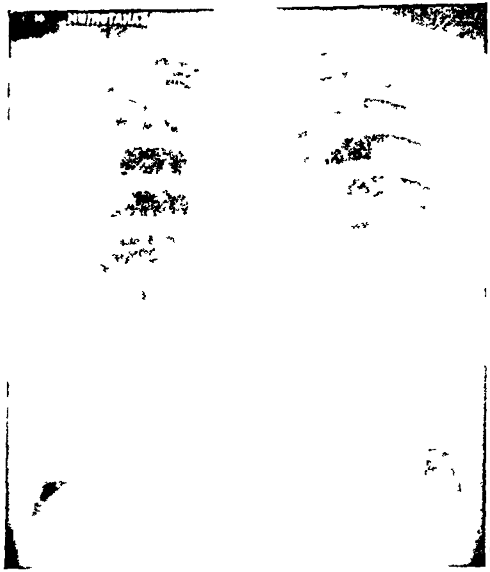

FIGURE 1

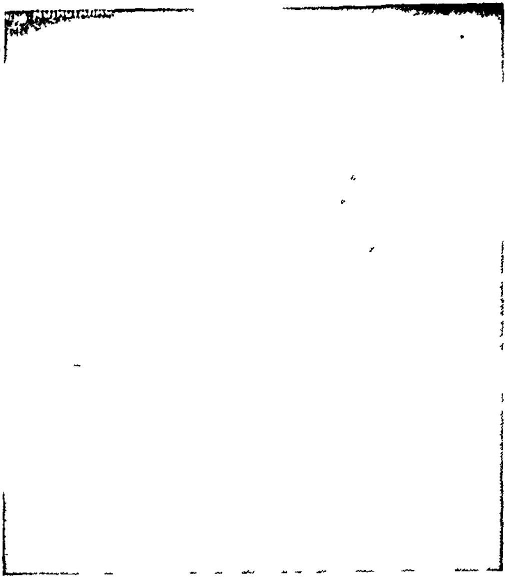

FIGURE 2

FIGURE 3

Figure 1 (Case 1): Roentgenogram of chest showing right middle lobe atelectasis along right cardiac border and slight density in left subhilar area. Most of the retracted lingula is hidden behind the heart.—*Figure 2:* Bronchogram of Case 1 showing bronchiectasis and bronchial clumping of the right middle lobe and lingula.—*Figure 3: PA* roentgenogram of chest of Case 1, three months postoperatively.

Case Reports

Case 1: A 53 year old white woman was admitted to the Mississippi State Sanatorium on March 30, 1955. She had been subject to "bronchitis" since childhood with frequent malaise, colds, fever and a productive cough. She had been seen here for productive cough, weight loss and malaise in September, 1934, at which time x-ray films revealed bilateral apical scarring but no other abnormalities.

In 1945 she started having hemoptyses and increased sputum. Bronchograms in August, 1947, revealed bronchiectasis of the right middle lobe which responded symptomatically to a regimen of postural drainage. In March of 1955 she had an attack of "virus pneumonia" with increased productive cough and hemoptysis. The sputum contained acid-fast bacilli for which she had been placed on streptomycin and PAS prior to admission.

Physical examination showed a well-developed, well-nourished woman (Figure 1). The lungs were clear and the remainder of the physical examination was essentially negative. Sputa on admission were negative and remained so. Other laboratory data were within normal limits. Repeat bronchograms (Figure 2) in July, 1955, revealed extensive bronchiectasis of the right middle lobe and of the lingula of the left upper lobe. Bronchoscopy on July 9, 1955 revealed erythema of the mucosa of the right middle lobe with pus coming from this orifice.

On August 21, 1955 the atelectatic, consolidated lingula was removed. Prominent lymph nodes were noted surrounding the hilum. The postoperative course was completely benign. On November 21, 1955 right middle lobectomy was performed. The lobe was shrunken and consolidated and a prominent collar of calcified nodes was found around the bronchus. The upper and lower lobes were completely free from obvious disease.

Pathologic examination of the lingula showed the specimen to be consolidated with a few small foci of cheesy consistency. Microscopic examination revealed residual nodules of chronic granulomatous inflammation and caseation compatible with tuberculosis. Adjacent tissues showed fibrosis and non-specific chronic inflammation.

Pathologic examination of the right middle lobe revealed marked dilatation of the bronchi, many of which were filled with gelatinous material. Microscopic examination showed bronchiectasis and non-specific chronic pneumonitis but no evidence of tuberculosis.

She was continued on antituberculous treatment and was discharged completely asymptomatic February 23, 1956.

Follow-up one year later showed she was doing extremely well with negative sputa and a clear chest x-ray film.

Case 2: A 49 year old white woman was admitted to the Mississippi State Sanatorium on December 12, 1954. Her past history revealed bronchopneumonia in 1940, and again in 1944, for which she entered a Sanatorium in California where bronchograms and gastric washings were reported as negative. In 1950 she had a severe pulmonary hemorrhage and bronchograms revealed bilateral bronchiectasis. In 1951 and again in 1953 she had "virus pneumonia." On October 30, 1954 she developed chills, fever and productive cough. Sputa were found to be positive for acid-fast bacilli and she was placed on streptomycin and PAS. One week later she developed thrombophlebitis of the left leg which persisted until admission here.

Physical examination revealed a slightly agitated woman with bilateral corneal opacities, enlarged cervical lymph nodes and moderate coarse rales over the right side of the chest. The liver presented two centimeters below the costal margin. The left leg was edematous, dry and scaly with a positive Homan's sign and tenderness along the course of the femoral vein. Sputum cultures were positive from January 18, 1955 until October 18, 1955 but negative thenceforth. Other laboratory data were normal. X-ray films showed infiltrations in the right upper lobe and both lower lung fields (Figures 4 and 5).

Bronchoscopy on September 8, 1955 showed slight erythema of the left main stem bronchus. On October 3, 1955 bronchograms revealed bronchiectasis of the middle lobe, the lingula of the left upper lobe (Figure 6) and the antero-medical segment of the left lower lobe. There was, in addition, minimal cylindrical bronchiectasis of the superior segment of the right lower lobe and the anterior segment of the right upper lobe.

As the sputa remained persistently positive she was placed on isoniazid and pyrazinamide just prior to resection. On October 31, 1955 left thoracotomy revealed nodularity and consolidation of the entire lingular segment with a similar process in the antero-medial basilar segment of the left lower lobe and these segments were excised. On April 9, 1956 right middle lobectomy was performed with no gross evidence of disease being found anywhere else. Thus, in view of her advanced age and limited respiratory reserve it was decided not to remove the superior segment of the right lower lobe or the anterior segment of the right upper lobe.

Pathologic examination of the left lung specimens revealed multiple adhesions, consolidation with small areas of caseation and a 2.5 centimeter cyst of the lingula. Microscopic examination revealed non-specific pneumonitis and bronchiectasis throughout with small areas of granulomatous reaction and caseation. Pathologic examination of the right middle lobe revealed it to be totally atelectatic and consolidated. Microscopic examination revealed marked bronchiectasis with both non-specific and granu-

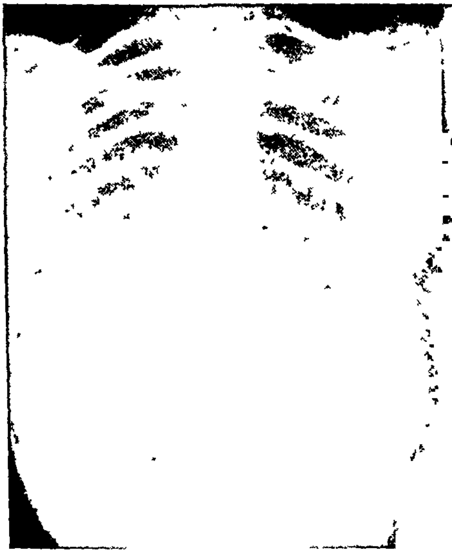

FIGURE 4

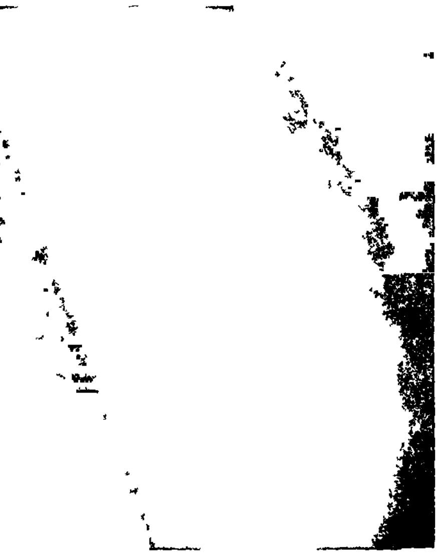

FIGURE 5

Figure 4 (Case 2): PA roentgenogram showing infiltrate along right cardiac border and along the left cardiac border in the subhilar area.—*Figure 5:* Right lateral chest roentgenogram of Case 2 showing typical consolidation of the right middle lobe.

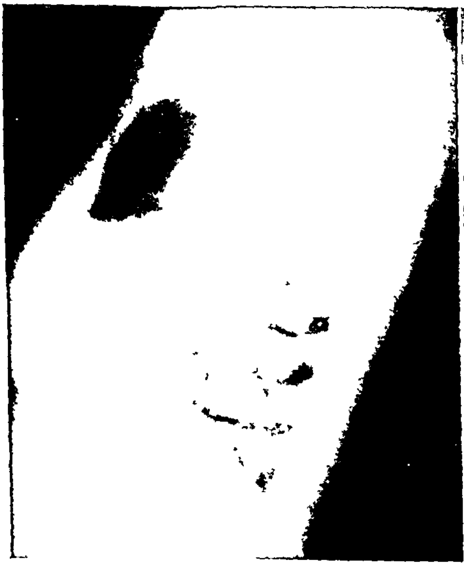

FIGURE 6

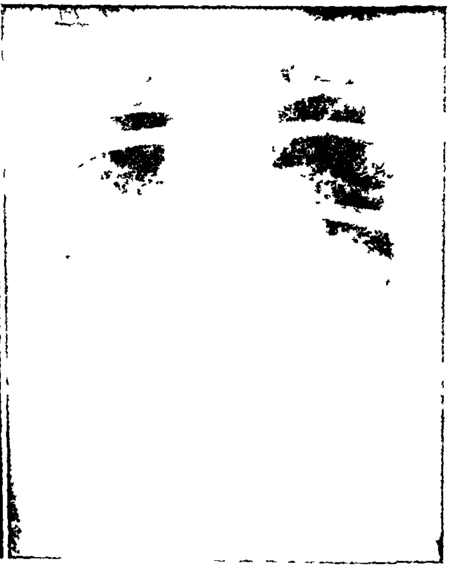

FIGURE 7

Figure 6 (Case 2): Left lateral bronchogram showing contracted, bronchiectatic lingula. A similar process can be seen faintly in the anteromedial segment of the left lower lobe.—*Figure 7* (Case 2): Chest x-ray film six months following second operation.

lomatous chronic inflammation. Five months postoperative she had another episode of blood streaking that subsided without clinical or radiologic sequelae. Sputa remained negative and it was thought the hemoptysis had come from residual bronchiectasis in the apex of the right lower lobe or anterior segment of the right upper lobe. She was discharged on November 25, 1956 in good health (Figure 7).

Discussion

Obstructive pneumonitis of a lobe or segment may be caused by an intrinsic lesion such as mucosal edema, fibrosis or plugging (mucoid impaction of Shaw),[6] or by extrinsic compression from lymph nodes or tumor. The right middle lobe is the most susceptible with the lingula being the next most frequently involved. Thus, Paulson and Shaw[7] record 32 cases of right middle lobe syndrome. Of the additional 12 cases of obstructive pneumonitis in their total experience, four involved the lingula. Samson[8] reported 17 cases of right middle lobe syndrome but only seven of right middle lobe bronchiectasis associated with contralateral bronchiectasis which had required resection. The only previously reported case of bilateral middle lobe syndrome found in an extensive perusal of the literature is case four reported by Rubin and Rubin[9] in their 16 cases of right middle lobe syndrome. This was a 29-year-old white man with consolidation and bronchiectasis of the right middle lobe and of the lingula which were demonstrated by x-ray films and bronchograms. No operation was performed in this case. The above cases are the first reported to have bilateral resections for obstructive pneumonitis of the right middle lobe and lingula. Many have been reported, of course, which had bilateral resections for bronchiectasis.

The etiology of nontuberculous bronchiectasis and the middle lobe syndrome are probably similar in that some degree of bronchial obstruction plays a prominent role in each. However, the middle lobe syndrome usually develops in older people and is associated with chronic lobar pneumonitis that is infrequent in the case of bronchiectasis. The middle lobe syndrome apparently persists as chronic pneumonitis because bronchial obstruction is more prolonged or permanent, while in bronchiectasis obstruction is transient or partial. This similarity is emphasized by the second case which had multiple segmental bronchiectasis in addition to obstructive pneumonitis of the right middle lobe, the lingula and one basilar segment.

Rubin and Rubin[9] present evidence that suggests a tuberculous origin of the compression collar of enlarged nodes around the middle lobe bronchus in each of their cases. Cohen[10] likewise stresses the frequency of right middle lobe atelectasis in elderly patients secondary to the reactivation of quiescent tuberculous adenitis which produces gradual compression and frequently perforation of the bronchi. However, many other cases have been found in which tuberculosis was excluded and the nodes were hypertrophied from non-specific inflammation.

Certainly the patients presented here had tuberculosis, the nature of which suggests reactivation in later life in the hilar nodes and not from the usual apical focus. Each had large calcified nodes around the bronchus on each side. It is interesting that the right middle lobe of the first case showed no granulomatous or caseous pathologic lesions suggesting tuberculosis, although the lingula showed typical tuberculous changes. It is, of course, a frequent finding in resected right middle lobes that the lymph nodes demonstrate tuberculosis and the parenchyma only non-specific chronic inflammatory changes.[11]

Symptomatology is related to bronchial narrowing, leading to recurrent attacks of pneumonia and frequently symptomatic bronchiectasis. There is usually a chronic cough, often spasmodic, occasionally severe, and intermittently productive. Blood streaking or frank hemorrhage is common, due either to the bronchiectasis or to bronchial ulceration by calcified lymph nodes. Persistent wheeze over the affected lobe is suggestive of this diagnosis.

Bronchoscopy may show bronchial narrowing, though often the stenosis is located distally and is demonstrable only by bronchograms or laminograms.

Treatment depends on many factors, such as chronicity of the process, symptomatology, and age and general condition of the patient. Early cases, especially with modern antibiotic therapy, may be completely reversible. In any chronic case, however, only resection is curative. Yet, as many chronic cases are completely asymptomatic and have remained so under observation for many years, the desire for radiologic improvement must be tempered by full evaluation of the patient.

SUMMARY

1. The term "bilateral middle lobe syndrome" has been used to describe concomitant chronic obstructive pneumonitis of the right middle lobe and its homolog, the lingula.

2. Two cases are presented, which are the first reported to have bilateral resections for this condition.

RESUMEN

1. El término "síndrome del lóbulo medio bilateral" se ha usado para describir la neumonitis obstructiva concomitantes del lóbulo medio derecho y de su homólogo que es la língula.

2. Se presentan dos casos que son los primeros relatados que han sufrido resección bilateral para esta afección.

RESUME

1. Le terme "syndrome bilatéral du lobe moyen" a été utilisé pour décrire la pneumonie chronique obstructive simultanée du lobe moyen et de son homologue, la lingula.

2. Les auteurs présentent deux cas, les premiers rapportés pour lesquels cet état a été suivi de résection bilatérale.

ZUSAMMENFASSUNG

1. Der Ausdruck "bilaterales Mittellappensyndrom" wurde benutzt zur Beschreibung der chronischen stenosierenden Pneumonitis, gleich-

zeitig vorkommend im rechten Mittellappen und in seinem Homologon, der Lingula.

2. Bericht über 2 Fälle, die die ersten sind, bei denen aus diesem Grunde eine beiderseitige Resektion vorgenommen wurde.

REFERENCES

1 Graham, E. A., Burford, T. H. and Mayer, J. H.: "Middle Lobe Syndrome," *Postgrad. Med.*, 4:29, 1948.

2 Rosenman, E.: "Acute, Transient Middle Lobe Disease," *Dis. Chest*, 27:80, 1955.

3 Packard, E. N.: "Massive Collapse (Atelectasis) Associated with Pulmonary Tuberculosis and Tumor," *Am. Rev. Tuberc.*, 18:7, 1928.

4 Zdansky, E.: "Der Mittellappen als Punctum minoris resistentiae der Lunge," *Wien. klin. Wschr.*, 58:197, 1946.

5 Brock, R. C.: "The Anatomy of the Bronchial Tree," *Oxford Medical Publications*, London, 1946.

6 Shaw, R. R.: "Mucoid Impaction of the Bronchi," *J. Thoracic Surg.*, 22:149, 1951.

7 Paulson, D. L. and Shaw, R. R.: "Chronic Atelectasis and Pneumonitis of the Middle Lobe," *J. Thoracic Surg.*, 18:747, 1949.

8 Samson, P. C.: In discussion of Paulson, D. L. and Shaw, R. R.: "Chronic Atelectasis and Pneumonitis of the Middle Lobe," *J. Thoracic Surg.*, 18:747, 1949.

9 Rubin, E. H. and Rubin, M.: "The Shrunken Right Middle Lobe," *Dis. Chest*, 18:127, 1950.

10 Cohen, A. G.: "Atelectasis of the Right Middle Lobe Resulting from Perforation of Tuberculous Lymph Nodes into Bronchi in Adults," *Ann. Int. Med.*, 35:820, 1951.

11 Head, J. R. and Moen, C. W.: "Late Nontuberculous Complications of Calcified Hilus Lymph Nodes," *Am. Rev. Tuberc.*, 60:1, 1949.

Why Do Tuberculous Patients Reactivate?

ALBERT R. ALLEN, M.D., F.C.C.P.
Selah, Washington

A review of the literature reveals uniform acceptance of the fact that a relatively large percentage of tuberculosis patients reactivate regardless of extent of disease,[8, 14, 19] type of treatment whether bedrest,[10] collapse therapy,[9] long[17] or short term chemotherapy or resection.[18] Further, it is accepted that the rate of relapse is usually in proportion to the extent of disease and the amount of physical activity carried on after discharge[12] and is inversely proportionate to the period of hospitalization, with relapse occurring more commonly in men[11] and most relapses occurring within the first three years after discharge. In an article regarding relapse in pulmonary tuberculosis published in 1928, Doctor H. Longstreet Taylor[20] stated that "all apparent relapses are not true relapses, but are evidence of the inherent chronicity of the disease in cases that have apparently improved for a time, but in which the diseased areas have neither healed by resolution nor been encapsulated by the slow process of connective-tissue hyperplasia, and after an uncertain interval, in which no change has been apparent, tubercle has once more begun to spread. . . . Premature discharge of the patient is but an invitation for trouble, since the length of treatment bears an inverse relationship to the percentage of relapses. Relapses are due to attacks of intercurrent disease, serious accidents, childbearing and lactation, to disobedience of the rules in regard to proper methods of work and play, to mental or physical fatigue, to a return to an unhygienic environment, and to many other devious wanderings from the straight and narrow way." . . . I disagree with this attitude which conveniently places responsibility for the relapse on the patient's shoulders and absolves the physician from all blame.

Materials and Methods

On June 1, 1952, we began our present treatment regimen, consisting of streptomycin, para-aminosalicylic acid and isoniazid used concurrently and continuously from admission to discharge, with early resectional surgery when indicated.[1, 2] This is a review of all patients treated between June 1, 1952 and June 1, 1955 who have reactivated as evidenced by positive cultures. There are 330 consecutive admissions with a proved diagnosis of tuberculosis either by positive culture or pathology, including all types of tuberculosis—primary, reinfection, pulmonary and extrapulmonary.[3] Drugs were given in the following dosage: streptomycin gm. 1 twice weekly or ½ gm. for children, para-aminosalicylic acid gm. 10 daily reduced according to weight in children, isoniazid 4 mg. per kilo of body weight daily. Operations were done on 142 patients and 188 were treated only with drugs. All patients received modified bed rest with full lavatory privileges plus cafeteria as soon as physically able and no collapse therapy either temporary or permanent was done or was rehabilitation training given. All returned to their former occupations upon discharge.[6] The average hospital stay for all patients was 212 days. Six treated medically died of tuberculosis during their hospital stay, while only three died after surgery, one with coronary occlusion, another with pulmonary emboli and one with primary atypical pneumonia. Ten others died of non-tuberculous disease during hospitalization and 14 are known to have died since discharge of non-tuberculous disease.

When drugs were used in courses it was recognized that they were less effective the second time they were given. Reactivation is an obvious indication that the drugs did not sterilize the lesion the first time they were used, therefore it is less likely that they would accomplish this the second try. Because of this, all who reactivated were resected if they were able to tolerate surgery. Those who had serious associated disease have since died so that between resections and autopsies we have pathology from 22 of 24 patients who reactivated. Twenty-three of the 24 returned to our hospital for treatment and the last case (renal tuberculosis) is discussed in detail later.

The radical change in treatment coupled with the fact that all patients have returned to their former occupations regardless of physical activity immediately upon discharge made close follow-up imperative.[6] In our previous experience using three gastric and sputum cultures done in this hospital on patients with x-ray changes characteristic of reinfection type tuberculosis and positive Mantoux, less than 6 per cent of these patients with negative cultures have shown x-ray progression or have had positive cultures within two years of their first admission.[4] Therefore an effort has been made to return as many as possible of these patients, treated since June 1, 1952, for a three day study.

TABLE I
FOLLOW-UP OF DISCHARGED PATIENTS

Number		Reactivations
139	X-ray film plus gastric culture	13
6	X-ray film plus sputum smear and culture	2
92	X-ray film plus clinic visit	8
15	X-ray film sent to us	0
13	Report sent to us	1
32	No follow-up	0
297	TOTAL	24

It is obvious from Table I that we would not have picked up 13 of these patients who were positive on gastric culture only had we depended upon sputum smear and culture and x-ray film change. It has been our experience that a patient may have positive gastric cultures for a year or more before he admits having sputum or before there is roentgenographic evidence of new disease. Only six patients admitted having sputum and two of them were positive. The balance were seen in clinics by a member of this hospital staff or x-ray films were sent to us for review or reports were sent from other clinics. All but 32 of the entire group (89 per cent) have been followed for an average of more than two years since discharge. If any of these 32 had been hospitalized elsewhere with tuberculosis, our x-ray films would have been requested so we would know about them. We assume some of them are dead and the remainder have not reactivated.

All ex-patients who have x-ray film changes are admitted to the hospital for evaluation. If they have negative cultures and the area clears quickly, they are discharged without further drug therapy. If the cultures are negative and they do not clear thoracotomy is indicated to establish the diagnosis because bronchogenic carcinoma is a good possibility.

The entire group of patients can be divided into those treated medically and surgically (Table II).

When we compare the medically and surgically treated groups there have been no reactivations in minimal disease and none of these patients were resected. When we compare those cases of moderately advanced tuberculosis who received drugs only with those who received drugs plus resection, the surgical group remained in the hospital only 45 days longer, they received about 90 days more of streptomycin and isoniazid and 30 days more PAS, yet the reactivation rate in the surgical group is less than 2 per cent and the reactivation rate in the medically treated group is over 10 per cent. When we compare those cases of far advanced tuberculosis who received drugs only with those who received drugs plus resection, the surgical group remained in the hospital only 14 days longer, they received about 30 days more streptomycin and isoniazid and two days more PAS, yet the reactivation rate in the surgical group is less than 5 per cent and the reactivation rate in the medically treated group is over 12 per cent. Thus those patients who were resected have had fewer reactivations despite the fact that they are hospitalized only a few days longer than the medically treated group and have only a few more days of drug therapy. Of the 17 fusions for bone tuberculosis, none has reactivated even though they have returned to their previous occupations.[7]

The one patient with renal disease who reactivated had one kidney removed some five years before admission here. The ureter from the other kidney is stenosed at the uretero-vesicular junction and has produced a hydronephrosis of the remaining kidney. His blood urea nitrogen and non-protein nitrogen are elevated. The stricture was opened surgically so it was possible to do a retrograde pyelogram by injecting dye rapidly into the bladder, yet the NPN and BUN remain elevated at least twice normal, his urine has contained tubercle bacilli for over a year and these tubercle bacilli are resistant to all commonly used drugs, including streptomycin, isoniazid and viomycin. He now has increasing urinary frequency in spite of continued drug therapy. Certainly obstruction to the outflow path has been a factor in the progression of his disease.

TABLE II

Medical								Surgical						
Number of Patients	Average Hospitalization In Days	Streptomycin	Isoniazid	PAS	Average Follow-Up In Months	Reactivations	Classification of Disease	Number of Patients	Average Hospitalization In Days	Streptomycin	Isoniazid	PAS	Average Follow-Up In Months	Reactivations
16	229	218	205	38	22	0	Primary Tuberculosis							
8	148	162	160	0	11	0	Tuberculous Meningitis							
2	43	182	182	43	12	0	Peritonitis and Adenitis							
4	144	214	214	144	21	1	Renal Tuberculosis	6	156	247	272	159	25	1
							Bone Tuberculosis	17	237	219	189	130	29	0
12	137	196	177	136	25	0	Minimal Pulmonary							
97	175	210	210	135	24	11	Moderately Advanced	55	220	300	293	165	23	1
49	248	277	279	163	23	7	Far Advanced	65	262	310	306	166	21	3

Bronchoscopies using a right angle and fore-oblique telescope have been done on 18 of these patients with pulmonary disease who reactivated. Sixteen had bronchitis as evidenced by increased redness with some edema. Nine had definite stenosis. Stenosis and bronchitis are important factors in reactivation of pulmonary tuberculosis. While bronchitis can be demonstrated in the pathology, bronchial stenosis is seldom reported because the bronchus is commonly cut and sutured at the site of the stenosis.

In analyzing 18 specimens from pulmonary resection and four from autopsy, five basic changes were found: cavity, caseous, tuberculous bronchitis, bronchiectasis and miliary, with two or more often present in the same specimen such as caseous and cavitary disease. Caseation was present in 14, tuberculous bronchitis in 13, cavitary disease in 12, miliary type disease in three and bronchiectasis in two.

The only selectivity between groups treated medically and those treated surgically was first, the 14 retired people who were treated medically because they were not good surgical risks (four of whom reactivated); and second, those who refused surgery during their first period of hospitalization (eight in this group). Five others were not considered for resection for the following reasons: two left against medical advice and their drug treatment was continued for the average time through the health department or private physician; one had essential hypertension but was resected successfully when she reactivated; two had such extensive tuberculosis that we felt resection was too risky during first hospitalization, but both were resected when they reactivated, one died of pulmonary embolus two days post-operatively. The balance of the 23 with pulmonary disease who reactivated (six) had disease which was primarily caseous and after routine anteroposterior tomographs we did not feel that resection was necessary during their first admission; the last patient in this group had renal tuberculosis with one kidney resected previously so the remaining kidney could not be removed.

In culturing resected specimens from patients who had negative gastric cultures before surgery only 11 per cent had positive cultures and another 11 per cent had positive smear and negative culture. Twelve of these resected specimens from reactivations have been cultured and eight (67 per cent) were positive.[5] It is evident therefore that reactivation occurs because of the presence of viable, virulent tubercle bacilli that are not reached by drugs.[15] If reactivation is to be prevented, the types of disease in which these organisms are harbored, namely caseous masses, cavitary disease and serious endobronchial change (bronchial stenosis, bronchiectasis and tuberculous bronchitis), must be resected.

Discussion

A certain percentage of tuberculous patients reactivate regardless of type of treatment and the extent of disease is a definite factor. In this group those with minimal tuberculosis have received drugs only for an average of 196 days and there have been no reactivations at the end of over two years of follow-up. In the cases with moderately to far advanced pulmonary tuberculosis, those treated with drugs plus resection have had fewer reactivations than those treated with drugs alone. This is true because the type of disease into which drugs cannot penetrate has been removed, namely caseous areas 2 cm. or more in diameter, cavities, bronchial stenosis, tuberculous bronchitis and bronchiectasis. Medlar[16] stresses several things that are of great importance and which have bearing upon what we see in our patients. First, reactivations come from necrotic debris; second, he has never seen a completely healed cavity; third, bronchiectasis peripheral to the stenosis contains debris with viable tubercle bacilli which cannot be completely cleared so that repair can take place.

These patients have not received the long term drug therapy given elsewhere. Such therapy may delay these relapses but will not prevent them as reported by D'Esopo. Because all tuberculous lesions tend to be avascular due to the endarteritis,[13] chemotherapy will be effective before there is extensive destruction, as seen in our minimal cases.

Routine anteroposterior tomographs taken of the entire chest at 1 cm. intervals after three months of chemotherapy will demonstrate most of the lesions which are commonly seen in reactivations and if a lesion that might cause reactivation is suspected then the patient should be bronchoscoped, using right angle and fore-oblique telescopes to find bronchial stenosis.

Most of our patients returned immediately to moderately or heavy work, requiring 2,000 to 3,000 calories per day, yet those doing lightest work—retired people—had the highest reactivation rate, 14 per cent. Our women had the lowest reactivation rate because they came to the hospital for treatment earlier in the course of the disease, they accepted surgery more readily than the men and few left against medical advice. Apparently pregnancy is no factor in reactivation since 18 of our women had 26 pregnancies with no relapse. In all of our reactivations, the ratio of men to women is 3 to 2, but this is almost the same proportion as admissions.

We used only modified bedrest consisting of two rest periods during the day, full lavatory and cafeteria privileges as soon as physically able. No collapse therapy of any kind was done.

A significant percentage of our patients came from the low economic level, many cannot read or write, and for them rehabilitation to lighter work is impossible for they do not have the mental ability to learn. If we order these patients to do no manual labor then they have no alternative but to receive public assistance the rest of their lives. In spite of the fact that we send all patients back to their previous occupations, our reactivation rate is lower than that reported in other institutions where extensive rehabilitation programs are carried on.

The time spent in a hospital is not as important as the treatment that is given during the hospital stay. The purpose of a tuberculosis hospital is to isolate patients while contagious and to treat them so that there is reasonable assurance that they will not reactivate. Since reactivation is due to the type of pathology present, it is the physician's responsibility to rule out or remove, if possible, these types of pathology. The period of hospitalization for all of these patients was 212 days, this was shortened to 159 days in 1955 and was reduced even further in 1956.

Resistant organisms other than those present on admission have not been a significant factor in reactivation because, using the three drug combination, resistant organisms do not begin to appear until after six months of drug therapy and the 120 original resections were done during the third to fourth month after starting drug therapy. Those patients who reactivated and could not be resected remained positive until death and they developed organisms resistant to all three drugs.

SUMMARY

Reactivation of tuberculosis is due to the presence of virulent viable tubercle bacilli that remain in the tissue. Because of the tendency of the blood vessels in the involved area to be obliterated, chemotherapy does not penetrate into the caseous areas and thick cavitary walls to sterilize these lesions. The other tendency of tuberculosis to obstruct the bronchi with tracheobronchitis prohibits the debris containing tubercle bacilli from being evacuated; therefore this is also a big factor in the reactivation. The extent of disease is a factor because the more extensive the disease, the greater the probability that these serious types of pathology are present. Since the type of pathology present is the main factor in reactivation, our results are as expected. Minimal tuberculosis responds well to drugs only, with no reactivations. In moderately and far advanced disease those patients with resection of these serious types of pathology have fewer reactivations than those who received drugs only. With anteroposterior tomographs and bronchoscopy, using right-angle and fore-oblique telescopes, most of these serious types of pathology can be detected, and it is the physician's responsibility to rule out or remove this pathology before the patient is discharged. Patients have positive gastric cultures for a year or more before they admit having sputum or have x-ray film evidence of new disease, so gastric cultures are necessary to pick up early reactivation. The old ideas that physical exertion, pregnancy, etc., are the causes of reactivation are not true.

RESUMEN

La reactivación de la tuberculosis se debe a la presencia de bacilos virulentos viables que permanecen en los tejidos. A causa de la tendencia de los vasos sanguíneos en el área comprometida, a obliterarse, la quimioterapia no penetra dentro de las áreas caseosas y a través de gruesas paredes caviarias para esterilizar estas lesiones. La otra tendencia de la tuberculosis a obstruir el bronquio por la traqueobronquitis impide que los desechos que contienen bacilos tuberculosos sean evacuados; por tanto, este es también un factor de reactivación. La extensión de la enfermedad es un factor por mientras más extensa es la enfermedad mayor es la probabilidad de que estas graves formas de patología se encuentren.

Puesto que el tipo de lesión patológica que sepresente es el factor mayor de reactivación, nuestros resultados son como se esperan. La tuberculosis mínima responde bien a las drogas solas. En la tuberculosis moderada y muy avanzada los enfermos con resección de estas formas, graves de patología tienen menos reactivaciones que los que sólo reciben drogas. Con las tomografías anteroposteriores y broncoscopías, usando telescopios forblicuos de ángulo recto, la mayoría de estas lesiones serias pueden ser descubiertas y es de la responsabilidad del médico descartar o resecar las lesiones antes de dar de alta a un enfermo. Los enfermos tienen cultivos de lavados gástricos por un año o más, antes de que admitan que tienen esputos positivos y tengan evidencias radiológicas de le enfermedad. Así, es necesario hacer lavados gástricos muy temprano para sorprender pronto las reactivaciones. Las ideas antiguas de que el ejercicio físico, el embarazo, etc., son la causa de la reactivación, no son ciertas.

RESUME

La réactivation de la tuberculose est imputable à la présence de bacilles tuberculeux virulents viables, qui restent dans les tissus. La tendance à l'oblitération des vaisseaux sanguins qui se trouvent dans la région atteinte fait obstacle à la pénétration de la chimiothérapie dans les zones caséeuses et dans les parois cavitaires épaisses. Ainsi ces lésions ne peuvent se stériliser. L'autre tendance du processus tuberculeux qui est l'obstruction bronchique par trachéobronchite empêche l'évacuation des débris contenant des bacilles tuberculeux, ce qui constitue également un facteur important dans la réactivation. L'extension de la maladie est un facteur à prendre en considération parce que plus l'affection est étendue, plus est probable l'existence de lésions graves. Le caractère des lésions étant actuellement le principal facteur de la réactivation, nos résultats sont ceux que nous attendions. La tuberculose minime répond bien aux seuls produits médicamenteux, sans réactivation. Dans la tuberculose à lésions modérées ou très avancées, les malades qui ont subi une résection ont moins de réactivations que ceux qui n'ont été traités que par les médications. La plupart de ces lésions graves peuvent être dépistées par des tomographies antéropostérieures, et des bronchoscopies, en utilisant des optiques à 90° et obliques. Le devoir du médecin est de juguler ou d'enlever ces lésions avant que le malade ne soit autorisé à sortir de l'hôpital. Les cultures de tubages sont positives un an et plus, avant que les malades ne connaissent l'évidence bactériologique ou radiologique d'une nouvelle atteinte, aussi les cultures de tubages sont-elles nécessaires pour dépister précocément une réactivation. Les vieilles idées sont inexactes, selon lesquelles les agents physiques, la grossesse, etc. . . . sont les causes de rechute.

ZUSAMMENFASSUNG

Reaktivierung der Tuberkulose ist die Folge der Anwesenheit von virulenten lebensfähigen Tuberkelbazillen, die im Gewebe bleiben. Wegen der Tendenz der Blutgefässe zur Obliteration in dem befallenem Bereich dringt die Chemotheraphie nicht in die käsigen Bezirke und in die dicken Kavenenwände ein, um diese Herde keimfrei zu machen.

Die andere Neigung der Tuberkulose zur Stenose der Bronchien mit Tracheobronchitis hindert die Tuberkelbazillenhaltigen Zelltrümmer daran, ausgeworfen zu werden; daher ist auch dieser Umstand eine erheblicher Faktor bei der Reaktivierung. Die Ausdehenung der Krankheit ist ein Faktor, denn je ausgedehnter der Prozess, desto grösser die Wahrscheinlichkeit, dass diese ernsthaften Arten von pathologischen Veränderungen vorliegen. Da der jeweils vorliegende Typ von pathologischer Veränderung der Hauptfaktor bei der Reaktivierung ist, sind unsere Ergebisse den Erwartungen entsprechend: die minimale Tuberkulose reagiert gut, wenn nur Medikamente gegeben werden, und ohne Reaktivierung. Bei mässig und bei weit fortgeschrittner Erkrankung zeigen diejenigen Kranken mit Resektion dieser ernsthaften pathologischen Veränderungen weniger Reaktivierungen als solche, die nur Medikamente erhalten hatten. Mit Hilfe von frontalen Schichtaufnahmen und mit der Bronchoskopie unter Verwendung von rechtwinkligen und schrägen Optiken lassen sich die meisten dieser ernsthaften pathologischen Veränderungen auffinden, und der Arzt ist dafür verantwortlich, diese Veränderungen, ehe der Patient entlassen wird, auszuschlissen oder zu beseitigen. Bei Patienten kommen positive Kulturen von Magensäften vor ein Jahr oder länger, ehe sie stationär aufgenommen werden mit positivem Sputum oder röntgenologischen Nachweis einer Neuerkrankung; deshalb ist kulturelle Verarbeitung vom Magensaft nötig, um die Beginnende Reaktivierung herauszufinden. Die bisherige Vorstellung, wonach körperliche Anstrengung, Schwangerschaft usw. die Ursachen der Reaktivierung sein sollen, treffen nicht zu.

REFERENCES

1 Allen, A. R., Marcy, G. E. and Yu, J. K.: "Conventional Therapy Versus the Continuous and Concurrent Use of Streptomycin, Isoniazid, and Para-aminosalicylic Acid Plus Early Surgery in the Treatment of Tuberculosis," *Dis. Chest*, 28:548, 1955.

2 Allen, A. R., Marcy, G. E. and Yu, J. K.: "The Continuous and Concurrent Use of Streptomycin, Para-aminosalicylic Acid, Isoniazid Plus Early Surgery in the Treatment of Tuberculosis," *Dis. Chest*, 26:41, 1954.

3 Allen, A. R., Marcy, G. E. and Yu, J. K.: "The Tuberculosis Problem Today," *Northwest Med.*, 54: 379:381, 1955.

4 Allen, A. R., Harmon, R. W. J., Klacsan, L. J. and Stewart, K. M.: The Accuracy of the Confirmatory Diagnosis of Tuberculosis," *Am. J. Med.* 22:904, 1957.

5 Allen, A. R.: "Why Drugs are Not Enough in the Treatment of Tuberculosis," *Arch. Int. Med.*, 98:463, 1956.

6 Allen, A. R.: "Ex-Tuberculosis Patient as an Employee," *Indust. Med. and Surg.*, 25:573, 1956.

7 Allen, A. R. and Stevenson, A. W.: "The Results of Combined Drug Therapy and Early Fusion in Bone Tuberculosis," *J. Bone and Joint Surg.*, 39A:32, 1957.

8 Alling, D. W., Lincoln, N. S. and Bosworth, E. B.: "The After-History of Pulmonary Tuberculosis: IV. Far Advanced Tuberculosis," *Am. Rev. Tuberc.*, 70:995, 1954.

9 Bogen, E. and Skillen, J.: "The Rehabilitation of Tuberculous Patients Following Major Thoracic Surgical Treatment," *Dis. Chest*, 26:558, 1954.

10 DeFriez, A. I., Patton, W. E., Welch, E. J. and Badger, T. L.: "Bed Rest in the Treatment of Pulmonary Tuberculosis," *New England J. Med.*, 250:39, 1954.

11 Farquaharson, M.: "Relapse in Pulmonary Tuberculosis," *Tubercle*, 33:242, 1952.

12 Ferguson, R. G.: "Follow-Up Information on 1,747 Tuberculosis Patients One to Seven Years after Discharge from a Sanatorium," *Am. Rev. Tuberc.*, 14:625, 1926.

13 Gardner, L. U.: "The Pathology of Artificial Pneumothorax in Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 10:501, 1925.

14 Lincoln, N. S., Bosworth, E. B. and Alling, D. W.: "The After-History of Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 70:15, 1954.

15 Machaness, G. B. and Smith, N.: "The Bactericidal Action of Isoniazid, Streptomycin and Terramycin on Extracellular and Intracellular Tubercle Bacilli," *Am. Rev. Tuberc.*, 67:322, 1953.

16 Medlar, E. M.: "The Behavior of Pulmonary Tuberculous Lesions," *Am. Rev. Tuberc.*, 71: Part II, 1955.

17 Raleigh, J. W., D'Esopo, N. D., Osgood, C. K. and Campbell, A. H.: *Relapse Following Chemotherapy for Pulmonary Tuberculosis.* Transactions N.T.A., 50th Annual Meeting, pp. 260, 1954.

18 Schlosser, R. J. and Jarvis, F. J.: "Resection Failures in Pulmonary Tuberculosis," *J. Thoracic Surg.*, 29:335, 1955.

19 Stephens, M. G.: "Pulmonary Tuberculosis Relapse and Mortality," *Am. Rev. Tuberc.*, 70:601, 1954.

20 Taylor, H. L.: "Relapse in Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 18:1, 1928.

Adrenocortical Pathway of Lobeline Protection in Some Forms of Experimental Lung Edema of the Rat*

D. F. J. HALMAGYI, M.D., A. KOVACS, M.D. and P. NEUMANN, M.D.
Szeged, Hungary

The protective effect of lobeline in pulmonary edema following a.) vagotomy, b.) ammonium chloride intoxication, c.) intravenous adrenaline, d.) intraperitoneal α-naphthylthiourea (ANTU) and e.) chloropicrin inhalation was described in a former paper.[1] These earlier results are summarized (Fig. 1). The mode of action of lobeline remained in this previous work unsettled. It became clear, however, that this protective effect of lobeline is entirely unrelated to its action on the respiratory centers. In this paper some observations concerning the mechanism of this rather surprising action of lobeline are reported. Most of this work was done on CLOP-induced edema of the lungs. This type of edema was preferred because of its well known irresponsiveness to any other drug than lobeline.[1]

Methods and Procedures

Three hundred and nineteen male and female albino rats weighing 150-350 grams were used throughout these experiments.

One hundred and seventy-seven rats were exposed to inhalation of 0.3 cc. 30 lit. CLOP for five minutes. The details of this method are given in our earlier publication.[1] Two animals were simultaneously exposed: the treatment or procedure under trial was applied to one of them while the other served as control.

The first injection of lobeline (Boehringer) consisted of an intraperitoneal dose of 30 mg./Kg. given immediately after the animals were removed from the gas chamber. This dose was followed by the subcutaneous administration of 20, 15, 10, 10 mg./Kg. lobeline every fifth minute.

Twenty-four rats pretreated with 10 mg./Kg. barbiturate (Sevenal), 0.66 cc./100 g. of a 6 per cent soltion of ammonium chloride was given intraperitoneally. Lobeline was given to half of them in a dose of 30-10 mg./Kg. subsequently every fifth minute.

Forty-nine rats were given 20 mg./Kg. ANTU intraperitoneally. (ANTU was dissolved in propylenglycoll). Lobeline was given to half of them immediately after the injection of ANTU in a dose of 20 mg./Kg. Every 15 minutes they received a further 10-15 mg./Kg. dose of lobeline.

Bilateral cervical vagotomy was carried out in 69 rats in ether anesthesia. Within a minute after completing the vagotomy lobeline treatment was started in half of the animals. The first dose consisted of 20 mg./Kg. subcutaneously, and a dose of 10-15 mg./Kg. was repeated at intervals of 10-20 minutes.

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*From the 1st Dept. of Medicine and Dept. of Pharmacology, University Medical School, Szeged, Hungary, and from the Toxicology Dept. of the Hungarian Army Medical Research Institute, Budapest.

Present addresses: Dr. Halmagyi, Pneumoconiosis Research Unit, Llandough Hospital, Cardiff, Great Britain; Dr. Kovacs, Organisch-Chemische Anstalt, Universitat Basel, Switzerland; Dr. Neumann, Vienna, Austria.

The animals were killed by crushing their cervical spine. Survival time, as calculated from the end of the gassing or from the time of intoxication were about the same in the trial and control groups.

The thorax was opened immediately after death. The heart, oesophagus, thymus and great vessels were carefully dissected off. The trachea was divided at a uniform level. The lungs were weighed to 0.01 g. Lung-body weight ratios were calculated: lung weight was expressed as per cent of body weight. This value will be further referred to as "lung weight."

Lung weight of normal untreated rats was found in this laboratory

The Protective Effect of Lobeline in Different
Forms of Experimental Pulmonary Oedema in the Rat

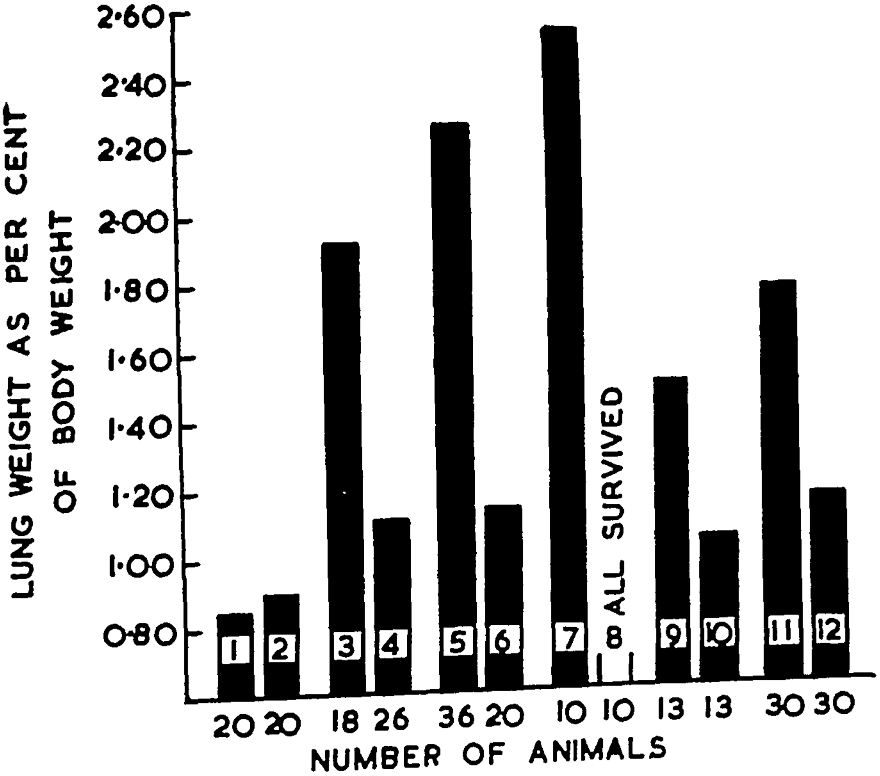

FIGURE 1

1. Normal, untreated controls
2. Normal, lobeline treated controls
3. Vagotomized, untreated
4. Vagotomized, lobeline treated
5. Intoxication with NH_4Cl
6. Intoxication with NH_4Cl, treated with lobeline
7. Intravenous adrenaline
8. Intravenous adrenaline and lobeline treatment
9. Intoxication with ANTU
10. Intoxication with ANTU and lobeline treatment
11. Intoxication with CLOP
12. Intoxication with CLOP and lobeline treatment

0.85 (± 0.07) per cent. Lung weight of intact, lobeline treated rats amounted 0.89 (± 0.06) per cent. In most of the cases measurement of lung weight was supplemented by histologic sections of the lungs. This method of assessing lung edema was found, however, less helpful in our hands.

Statistical evaluation of the results was carried out according to well known formulae.[2]

Adrenalectomy was carried out in 155 of the 319 animals. Bilateral adrenalectomy was done and was followed in most of the cases by a four day period of rest. During these the animals were kept—if not stated otherwise—under a regime of salt water. They all remained in good condition. Others were given desoxycorticosterone acetate (decortone, Ciba), cortisone or hydrocortisone (adresone or hydroadresone, Organon).

In 12 rats experiments were started immediately following the removal of both adrenals. Hypophysectomy was carried out in five. Experiments were started 100 days following this procedure. After killing the animals completeness of hypophysectomy was carefully controlled.

The adrenal medulla was extirpated in seven. Investigations were made 100 days subsequent to medullectomy. A careful post mortem was done in each case which included weighing and microscopic examinations of the adrenal cortex. The weight of the adrenal cortex exceeded in each animal 12 mg./Kg. 100 g. body weight. The finer structure of the cortex was found to be normal.

Results

Results are summarized in Tables I and II and Figures 2 and 3.

Mean lung weight of 26 normal gassed but otherwise untreated animals amounted to 1.29 (Group I of Table I), while that of 11 lobeline treated gassed rats was found 0.90 (Group II of Table I). The difference between these two mean lung weights was statistically significant ($t=3.4975$; $P<0.01$). No microscopic evidence of edema formation could be detected in the lungs of lobeline treated gassed rats.

Mean lung weight of 16 adrenalectomized gassed lobeline treated animals amounted to 1.78 (Group IV of Table I). This value was superior to the mean lung weight of Group III of Table I which consisted of adrenalectomized gassed but otherwise untreated rats.

Mean lung weight of 5 hypophysectomized, CLOP-poisoned lobeline treated rats proved to be only slightly elevated (Group V of Table I).

A 4 per cent solution of formaldehyde was given to four intact rats subcutaneously, three times within 48 hours. On the third day the animals were put into the gas chamber. Their mean lung weight was found to be 1.93, highly elevated (Group VI of Table I).

Corticotrophine (Organon) was injected intravenously to four healthy rats 30 minutes prior to gassing. Lung edema formation occurred in all animals, their mean lung weight was 1.62 (Group VII of Table I).

Corticotrophine Z (Organon) was given subcutaneously to 33 intact rats 24 hours prior to CLOP intoxication. Twenty I.U. was given to 11 rats, 40 I.U. to 17, while the rest received 60 I.U. of the long-acting corticotrophine. Pulmonary oedema occurred in all of them (Group VIII, a.b.c., Table I). The mean lung weight of the total Group VIII of Table I did not significantly differ from that of Group I of Table I ($t = 0.7573$; $P = 0.50$).

Noradrenaline (Jenapharm) was given to eight adrenalectomized rats in a dose of 50 micrograms prior to CLOP poisoning. At the end of the gassing procedure a dose of 30 micrograms was given followed by another dose of 20 micrograms five minutes later. The development of unusually

TABLE I

ROLE OF THE ADRENALS IN THE FORMATION OF PULMONARY OEDEMA CONSEQUENT TO CHLOROPICRIN INHALATION AND IN THE MECHANISM OF THE PROTECTIVE EFFECT OF LOBELINE

No.	Group	Treatment		Number of Animals	Weight of Animals, g.	Relative Lung Weight	Time of Survival Mins.
		Lobeline	Other				
I.	*normals*	—	——	26	258 (±13)	1.29 (±0.07)	20 (± 1)
II.	normals	+	——	11	236 (±16)	0.9 (±0.03)	36 (± 7)
III.	adrenalectomy	—	——	7	152 (±21)	1.64 (±0.14)	19 (± 4)
IV.	adrenalectomy	+	——	16	166 (±16)	1.78 (±0.13)	18 (± 5)
V.	hypophysectomy	+	——	5	167 (±11)	1.05 (±0.02)	20 (± 3)
VI.	normals	—	formaline stress	4	126	1.93	21
VII.	normals	—	ACTH 25 I.U., i.v.	4	150	1.62	26
VIII.	a normals	—	ACTH-Zinc 20 I.U., s.c.	11	286 (±21)	1.27 (±0.16)	22 (± 1)
	b normals	—	ACTH-Zinc 40 I.U., s.c.	17	242 (±16)	1.31 (±0.17)	20 (± 1)
	c normals	—	ACTH-Zinc 60 I.U., s.c.	5	190 (16)	1.64 (0.58)	20 (2)
IX.	adrenalectomy	+	noradrenaline	8	226 (±12)	2.10 (±0.32)	9 (± 2)
X.	medullectomy	+	——	7	253 (±20)	0.90 (±0.04)	31 (±18)
XI.	adrenalectomy	+	DOCA, 2 mg./die	17	190 (±13)	1.59 (±0.12)	17 (± 2)
XII.	adrenalectomy	—	Adresone 50-100 mg./die	10	210 (±12)	1.34 (±0.07)	21 (± 1)
XIII.	adrenalectomy	+	Adresone 5-100 mg./die	17	186 (± 9)	0.89 (±0.04)	16 (± 2)
XIV.	adrenalectomy recent	+	——	12	230 (± 5)	1.16 (±0.06)	19 (± 2)

Numbers in parenthesis represent standard deviation of the mean.

severe lung edema was observed in all animals: mean lung weight was 2.10 (Group IX of Table I).

Seven medullectomized rats were poisoned with CLOP and subsequently treated with lobeline. Neither macroscopic nor microscopic edema was observed in any of these animals: their mean lung weight remained normal: 0.90 (Group X of Table I).

Desoxycorticosterone acetate (DOCA) was administered to 17 adrenalectomized rats in a dose of 2 mg. daily for five days. The animals were gassed on the fifth day and lobeline treatment was subsequently started. Mean lung weight was 1.59: significantly elevated (Group XI of Table I).

Cortisone and hydrocortisone were given to 10 adrenalectomized rats in a dose of 50 resp. 100 mg. daily for four days. The animals were gassed on the fourth day, six hours following the last injection of the cortical

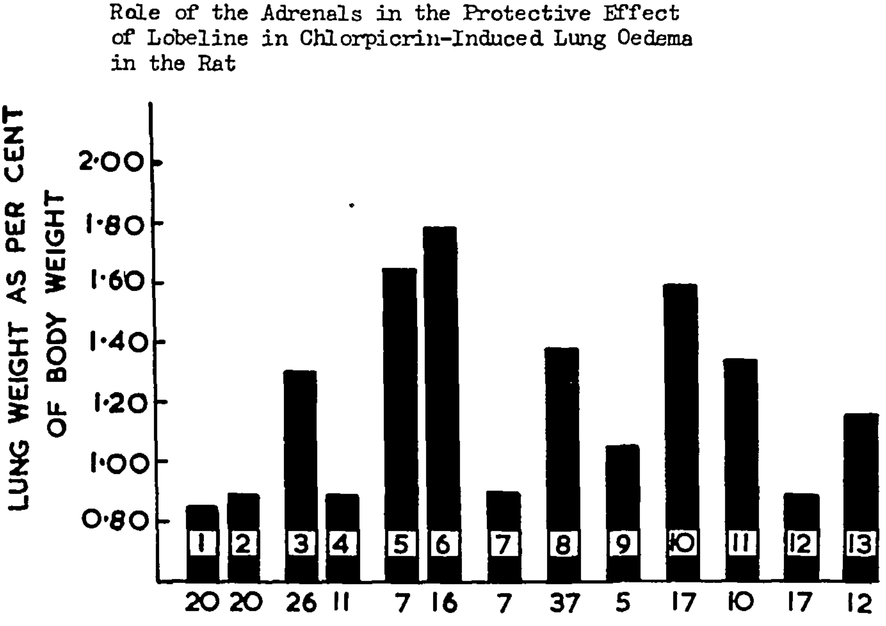

FIGURE 2

1. Normal untreated controls
2. Normals treated with lobeline
3. Normal, untreated, gassed rats
4. Normal, lobeline-treated, gassed rats
5. Adrenalectomized, untreated, gassed rats
6. Adrenalectomized, lobeline-treated, gassed rats
7. Medullectomized, lobeline-treated, gassed rats
8. Normal, ACTH-treated, gassed rats
9. Hypophysectomized, lobeline-treated, gassed rats
10. Adrenalectomized, lobeline-treated, gassed rats, maintained on DOCA (2 mg./day)
11. Adrenalectomized, untreated, gassed rats maintained on cortisone (50-100 mg./day)
12. Adrenalectomized, lobeline-treated, gassed rats maintained on cortisone (2-10 mg./day)
13. "Recent" adrenalectomy followed by gassing and lobeline treatment

extract. Inhalation of CLOP resulted in pulmonary edema: mean lung weight was 1.34 (Group XII of Table I).

Seventeen adrenalectomized rats were given a single injection of cortisone resp. hydrocortisone. The dose amounted to 100, 50, 25, 10, and 5 mg. subcutaneously. Six hours following this injection the animals were exposed to inhalation of CLOP, which was followed by the administration of lobeline. In no case did pulmonary edema appear. Mean lung weight was 0.89 and no histologic evidence of edema formation could be detected (Group XIII of Table I).

Gassing was carried out within 60 minutes following the removal of both adrenals in 12 rats (Group XIV of Table I). Subsequent to gassing lobeline treatment was started. A varying degree of lung edema formation occurred, their mean lung weight did not differ significantly from that of Group II of Table I ($t = 1.1623$; $0.20 < P < 0.30$).

This series of experiments are in a more simple form summarized in Figure 2.

ANTU was given to 24 intact and 25 adrenalectomized rats (Group I of Table II). Lobeline was administered subsequently to 14 intact and 15 adrenalectomized animals. The protective effect of lobeline was not influenced by the removal of both adrenals in this series: the difference between the resulting mean lung weights of the intact and adrenalectomized subgroups was statistically not significant.

Ammonium chloride was given to 12 intact and 12 adrenalectomized rats and all were treated with lobeline subsequently (Group II of Table II). There was no difference in the resulting mean lung weight of the two subgroups: both remained normal (0.95 and 0.89 respectively).

Bilateral cervical vagotomy was carried out in 38 intact and 31 adrenalectomized rats (Group III, Table II). Adrenalectomy itself failed to influence the development of vagotomy-induced lung edema: mean lung weight of the first and second subgroup amounted to 1.37 and 1.38 respectively. Lobeline treatment was, however, by far more effective in the intact subgroup (mean lung weight: 1.03) than in the adrenalectomized rats (mean lung weight 1.25). The difference between these two subgroups was statistically significant ($t = 2.3431$; $0.05 > P > 0.02$).

This series of experiments are in a more simple form summarized in Figure 3.

Discussion

Results of Groups I and II of Table I corroborate our earlier findings (1) concerning the protective effect of lobeline in CLOP edema of the lungs.

Lung weight of adrenalectomized gassed animals (Group III of Table I) exceeded significantly that of normals and remained practically unchanged following lobeline treatment (Group IV of Table I). These observations seemed therefore to permit the conclusion that a.) CLOP edema of the lungs is rendered more severe by the absence of the adrenals, b.) the adrenals play an indispensable role in establishing the protective effect of lobeline.

A slight number of observations reported by various authors speak in favour of the fact that an increased secretory activity of the adrenal cortices may prevent or ameliorate experimental lung edema. Selye[3] stated that in nephrectomized rats pulmonary edema subsequent to saline infusions could be prevented by the administration of 10 mg. of histamine. In another paper Selye[4] and Halpern, Cruchaud, Vermeil, and Roux[5] pointed out that pretreatment with a minute dose of adrenaline prevented the appearance of lung edema following a large dose of adrenaline. Testoni and Lomeo[7] stated that animals surviving a large dose of adrenaline (the survival was affected by the simultaneous administration of a sympatholytic drug) reach a certain degree of resistance to CLOP edema of the lungs. Koenig and Koenig[6] observed that in their cases formaline-stress inhibited the appearance of pulmonary edema consequent to ammonium chloride intoxication.

We were unable to support any of these observations. Pretreatment with adrenaline did neither prevent nor reduce pulmonary edema due to adrenaine or CLOP (unpublished material). Ammonium chloride edema—according to further unpublished experiments—remained unifluenced in formaline-stressed animals.

Adrenalectomy has an opposite effect in pulmonary edema due to oxygen poisoning:[15] it protects animals against the pulmonary consequences of high oxygen pressure. This however seems to be rather a special characteristic of this type of intoxication.

Recently, some clinical observations were reported concerning the beneficial effect of Prednisolone in more chronic types of lung edema in patients suffering from chronic congestive heart failure.

We were unable to obtain protection by stimulation of the adrenal cortices with formaline stress (Group VI of Table I), or by injecting immense doses of corticotrophine (Groups VII and VIII, Table I) in pulmonary edema following inhalation of CLOP. Serafini and Scapellato[13] have

TABLE II
ROLE OF THE ADRENALS IN THE DEVELOPMENT OF LOBELINE PROTECTION IN SOME FURTHER TYPES OF EXPERIMENTAL LUNG EDEMA

No. of Group	Form of Edema	Adrenals	Lobeline Treatment	No. of Rats	Mean Body Weight, g.	Survival Time, Min.	Lung Weight, Per Cent of Body Weight
I	ANTU	intact	withheld	10	127	190 (± 5)	1.33 (±0.04)
		intact	given	14	162	123 (± 5)	0.97 (±0.04)
		removed	withheld	10	178	187 (± 5)	1.49 (±0.07)
		removed	given	15	183	152 (± 6)	1.06 (±0.04)
II	NH_4CL	intact	given	12	176	33 (± 2)	0.95 (±0.08)
		removed	given	12	250	34 (± 3)	0.89 (±0.04)
III	vagotomy	intact	withheld	21	159	110 (±12)	1.37 (±0.08)
		intact	given	17	163	80 (± 8)	1.03 (±0.04)
		removed	withheld	16	178	114 (±10)	1.38 (±0.09)
		removed	given	15	154	70 (± 6)	1.25 (±0.07)

Numbers in parenthesis mean standard deviation.

either failed to inhibit the occurence of adrenaline lung edema in rabbits by administration of 5-10 I.U. of corticotrophine.

In view of the fact that stimulation of the adrenal cortex even by extreme doses of physiologic and pharmacologic substances remained absolutely ineffective in inhibiting CLOP-edema it seemed unlikely that lobeline protection would be due simply to adrenocortical hyperfunction. This suggestion was further emphasized by our results obtained in hypophysectomized rats (Group V, Table I). In these animals lobeline remained effective. Some other mechanism, rather independent of the anterior pituitary had to be searched for.

Anitchkow[8] and Kuznetzow[9] demonstrated years ago that lobeline increases the secretion of adrenaline. It was attempted therefore to investigate the signficance of the adrenal medulla in the protective effect of lobeline. Nor-adrenaline—as indicated in Group IX of Table I—rather increased lung edema formation in CLOP-poisoned adrenalectomized rats.

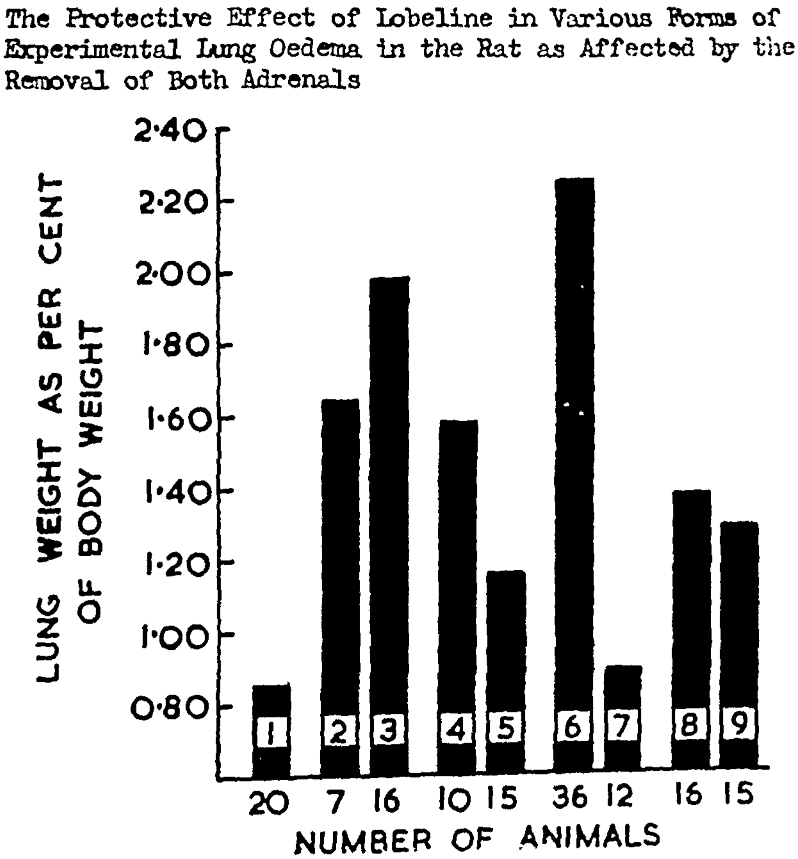

FIGURE 3

1. Normal, untreated controls
2. Adrenalectomized, untreated, gassed rats
3. Adrenalectomized, gassed, lobeline-treated rats
4. Adrenalectomized, ANTU-poisoned, untreated rats
5. Adrenalectomized, ANTU-poisoned, lobeline-treated rats
6. Normal, NH_4Cl-poisoned, untreated rats
7. Adrenalectomized, NH_4Cl-poisoned, lobeline-treated rats
8. Adrenalectomized, vagotomized, untreated rats
9. Adrenalectomized, vagotomized, lobeline-treated rats

On the other hand, lobeline was found to be fully effective in medullectomized animals (Group X of Table I). These observations seemed to indicate the conclusion that the adrenal medulla has no part in the mechanism of lobeline action.

In the next three groups of experiments the effect of adrenal cortical steroids was investigated. All these were carried out in adrenalectomized animals.

Extreme amounts of cortisone and hydrocortisone failed to influence lung edema formation (Group XII of Table I). DOCA given to adrenalectomized animals was ineffective in reestablishing lobeline protection (Group XI of Table I). On the other hand if lobeline was administered to adrenalectomized, cortisone treated rats (Group XIII of Table I), inhalation of CLOP failed to result in lung edema: mean lung weight in these rats was identical to that of intact, lobeline-treated, gassed animals (Group II of Table I). The protection was equally complete whatever the dose of cortisone has been between 5-100 mg. The effect of smaller doses of cortisone was not investigated. The effect of cortisone preadministration depended only from the time of the injection: it had to be given not more than six hours before the experiments.

From these experiments it was concluded that both lobeline and cortisone if given separately to adrenalectomized rats are ineffective in preventing pulmonary edema. These data support the concept that though an intact adrenal cortex is essential for the appearance of lobeline protection, cortisone has a supporting role and not an obligatory action.[14] A somewhat similar observation was recently reported by Kelmen[12] who stated that the presence of cortisone permitted to maintain the permeability inhibiting action of salicylates on the hind-paw edema of adrenalectomized rats. In his experiments however larger doses of cortisone were necessary.

Rat adrenal cortices secrete mostly aldosterone and corticosterone:[11] cortisone is secreted only in small amounts.[10] It remains still to be settled which of these three substances is responsible for the permissive action described above.

Mean lung weight of rats in which CLOP-inhalation was carried out immediately subsequent to adrenalectomy (Group XIV of Table I) was inferior to group IV and equal to Group I of Table I. This seems to support the concept that the amount of prefabricated cortical hormones is insufficient to permit lobeline protection.

Does the same mechanism of lobeline action apply to other types of lung edema? The answer to this question was found disturbing.

It is generally accepted that the mechanism of ANTU-edema is much similar to that of CLOP-edema of the lungs. We therefore turned our first attention to ANTU. (Group I of Table II). ANTU edema was found somewhat more severe in adrenalectomized rats. (The difference was however statistically not significant). Adrenalectomy, to our surprise, failed to inhibit the protective effect of lobeline: the extent of lobeline protection was similar both in intact and in adrenalectomized animals. A similar result was obtained in ammonium chloride intoxication where lobeline remained fully effective in adrenalectomized rats (Group II of Table II), and in aderenaline-edema (unpublished): the protection afforded by lobeline in adrenaline lung edema was unchanged in the absence of the adrenals. In these two latter groups however one could always argue that these large doses of lobeline have a ganglionic blocking effect. Ganglionic blockers are well known to inhibit ammonium chloride and adrenaline edema. Logically it was therefore expected that the same will happen in vagotomy-induced lung edema. The contrary has however occurred (Group III of Table II). Removal of both adrenals failed to influence edema formation in vagotomized animals. Despite expectation, no lobeline protection was observed in adrenalectomized animals.

Does the difference in the mechanism of lobeline protection justify a conclusion on the genesis of different types of lung edemas? This and many other points of this work can not be answered at present.

SUMMARY

Large doses of lobeline inhibit lung edema formation in chloropicrin (CLOP) poisoned rats. No protection was observed if lobeline was given to adrenalectomized animals. Hypophysectomy, adrenal medullectomy did not interfere with the protective effect of lobeline.

Stimulation of the adrenal cortex of intact rats by formaline stress or by the administration of adrenocorticotropic hormones, administration of desoxycorticosterone acetate or cortisone to adrenalectomized rats failed to influence lung edema formation even if given in extremely large doses.

Lobeline was fully effective in preventing pulmonary edema in adrenalectomized rats if the animals were given a pretreatment of cortisone. This observation supports the concept that though an intact adrenal cortex is essential for the appearance of lobeline protection, cortisone has a supporting role and not an obligatory regulatory action.

The presence of the adrenals were not necessary to permit lobeline protection in α-naphthyl-thiourea (ANTU), ammonium chloride, and adrenaline induced lung edema.

Lung edema in rats subjected to bilateral cervical vagotomy did not respond to lobeline in the absence of the adrenals.

Our thanks are due to Messrs. Organon Ltd. (Oss, The Netherlands) for a generous supply of hormone preparations. Invaluable suggestions and help given by Dr. E. Kelemen is gratefully acknowledged. Funds for this work were made available by the Army Medical Research Institute through the interest of Col. Dr. I. Kenez.

RESUMEN

En las ratas intoxicadas con cloropicrina (CLOP) la formación del edema se inhibe mediante grandes dosis de lobelina. Si la lobelina se dió en animales adrenalectomizados no se observó que la lobelina protegiese. La hipofisectomía, la medulectomía adrenal no interfirieron el efecto protector de la lobelina.

La estimulación de la corteza suprarrenal en ratas intactas, por medio de stress producido por la formalina o por la administración de hormonas

adrenocorticitrópicas, administración de desoxicorticosterona (acetato) o cortisona a las ratas adrenalectomizadas no influyóen la formación del edema aún dadas a dosis extremadamente altas.

La lobelina fué completamente efectiva para prevenir el edema pulmonar en las ratas adrenalectomizadas si a los animales se les dió un tratamiento previo con cortisona. Esta observación apoya el concepto de que aunque un cortez intacto es esencial para que haya protección con la lobelina, la cortisona tiene un papel de soporte en el edema pulmonar producido por L-naftil-tiourea (ANTU), el cloruro de amonio, y por la adrenalina.

El edema pulmonar en ratas sujetas a vagotomía cervical bilateral no respondió a la lobelina en ausencia de suprarrenales.

RESUME

De fortes doses de lobéline empêchent la formation d'oedème pulmonaire chez les rats empoisonnés par le chloropicrine (CLOP). On n'observa aucune protection si la lobéline est donnée à des animaux après surrénalectomie. L'hypophysectomie et l'ablation médullo-surrénalienne n'empêchent pas l'effet protecteur de la lobéline.

En l'absence de lobéline, la stimulation du cortex surrénal chez les rats indemnes, par des injections de "formaline" ou par l'administration d'hormones adrénocorticotropes, aussi bien que l'administration de grandes doses de cortisone (desoxycorticosterone) chez les rats ayant été surrénalectomisés ne purent empêcher le développement d'oedème pulmonaire.

La lobéline est capable d'empêcher l'oedème pulmonaire chez les rats surrénalectomisés traités par la cortisone.

Un travail ultérieur est nécessaire pour préciser le mécanisme exact de l'effet protecteur de la lobéline dans l'oedème pulmonaire.

ZUSAMMENFASSUNG

Hohe Dosen von Lobel in hemmen das Auftreten von Chlorpicrin-Lungenoedem bei Ratten. Diese Schutzwirkung wird durch Adrenalektomie aufgehoben, blieb jedoch durch Hypophysektomie unbeeinflusst.

Reizung der Nebennierenfunktion durch Formalin-Stress oder durch hohe Dosen des adrenocorticotropen Hormons, Verabreichung hoher Dosen von Cortison oder Desoxycorticosteron hatte die Entwicklung des Chlorpicrin-Lungenoedems nicht beeinflusst.

Die Lobelin-Schutzwirkung bei adrenalektomisierten Tieren wurde durch Cortison-Vorbehandlung wiederhergestellt. Es scheint als ob die Nebennierenrinde über eine unentbehrliche, jedoch keine regulative Rolle verfügte.

Eine ungestörte Lobelin-Schutzwirkung war auch nach Entfernung der Nebennieren bei α-Naphthyl-thioharnstoff-Oedem, bei Ammonium chlorid Oedem und bei Adrenalin-Oedem beobachtet. Entfernung der Nebennieren verhinderte jedoch die Lobelin-Schutzwirkung bi Vagotomie-Lungenoedem.

REFERENCES

1 Halmágyi, D., Kovács, A., Neumann, P. and Kenéz, I.: "Protective Effect of Lobeline in Experimental Pulmonary Edema," *Arch. Internat. Pharmacodyn.*, 106:17, 1956.

2 Fisher, R. A.: *Statistical Methods for Research Workers.* 1950, Oliver and Boyd, London.

3 Selye, H.: Über den Einfluss der Alarmreaktion und der Histaminbehandlung auf den Wasserstoffwechsel bei Nierenschädigung," *Klin. Wschr.*, 17:666, 1938.

4 Selye, H.: "The Prevention of Adrenaline Lung Edema by the Alarm Reaction," *Am. J. Physiol.*, 122:347, 1938.

5 Halpern, B. N., Cruchaud, S., Vermeil, G. and Roux, J. L.: "Étude pathogénique et thérapeutique de l" oedéme aigue du poumon expérimental," *Arch. Internat. Pharmacodyn.*, 42:98, 1948.

6 Koenig, H. and Koenig, R.: "Studies on the Pathogenesis of Ammonium Pulmonary Edema," *Am. J. Physiol.*, 158:1, 1949.

7 Testoni, F. and Lomeo, G.: "Azione protettiva delle dosi edemigene di adrenalina verso 1" edema polmonare acuto da cloropicrina nel coniglio," *Ormonologia*, 14:1, 1954.

8 Anitchkow, S. W.: "Über die Wirkung des Lobelins auf die Isolierte Nebenniere," *Arch. exper. Pathol. Pharmakol.*, 118:242, 1926.

9 Kusnetzow, A. I.: "Vergleichende Wirkung der Gangliengifte auf die Funktion der isolierten Nebenniere," *Arch. exper. Pathol. Pharmakol.*, 135:333, 1928.

10 Bush, I. E.: "Species Differences in Adrenocortical Secretion," *J. Endocrin.*, 9:95, 1953.

11 Singer, P. and Stack-Dunne, M. P.: "The Secretion of Aldosterone and Corticosterone by the Rat Adrenal," *J. Endocrin.*, 12:130, 1955.

12 Kelemen, E.: "The Role of Cortisone in a Permeability-Response of Salicylate-Injured Adrenalectomized Rats," *Acta Med. Hung.*, 9:125, 1956.

13 Serafini, V. M. and Scapellato, L.: "Ormone adreno-corticotropico ipofisario ed edema pulmonare acuto da adrenalina," *Boll. Soc. Ital. Biol. Sper.*, 28:1395, 1952.

14 Ingle, D. J.: "The Functional Interrelationship of the Anterior Pituitary and the Adrenal Cortex," *Ann. Int. Med.*, 35:652, 1951.

15 Gerschman, R., Gilbert, D. L., Nye, S. W., Nadig, P. W. and Fenn, W. O.: "Role of Adrenalectomy and Adrenal Cortical Hormones in Oxygen Poisoning," *Am. J. Physiol.*, 178:346, 1954.

SECTION ON CARDIOVASCULAR DISEASES

Ebstein's Malformation of the Tricuspid Valve

Study of a Case Together with Suggestion of a New Form of Surgical Therapy

SAMUEL W. HUNTER, M.D. and C. WALTON LILLEHEI, M.D., F.C.C.P.
Minneapolis, Minnesota

Ebstein's malformation of the tricuspid valve was first described by Wilhelm Ebstein in his publication of 1866.[1] The salient features of this defect which are relatively constant are: (1) A dilated right atrium usually to a severe degree, (2) Downward displacement of the tricuspid valve into the right ventricular portion of the heart, (3) Severe distortion of the posterior and septal leaflets of the tricuspid valve by this downward displacement of their attachments. There may or may not be variable associated defects such as a patent foramen ovale or atrial septal defect, fenestrations of the deformed tricuspid leaflets, diminution in the right ventricular capacity, evidence of tricuspid insufficiency, and conduction defects consisting of right bundle branch block with prolonged PR interval.

This association of congenital defects has been recognized rather infrequently since Ebstein's description so that in 1937 Yates and Shapiro, reviewing the literature, added the 16th reported case.[2] Kilby and co-workers[3] recently re-reviewed the literature and added five more cases along with one patient surviving closure of the atrial communication.

It is of interest in the light of the frequent association of conduction defects with this malformation that detailed studies by Yates and Shapiro of the right and left bundles of His revealed no abnormalities of the left bundle branch, and although the course of the right bundle branch was somewhat abnormal it conformed in a general way to that of the normal heart.

Thus far medical treatment has consisted of non-specific management of complications as they appear. These have been decompensation (frequently associated with the onset of cyanosis) and arrhythmias. A significant number of these patients die suddenly presumably of ventricular

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From the Department of Surgery and Variety Club Heart Hospital, University of Minnesota Medical School, Minneapolis.

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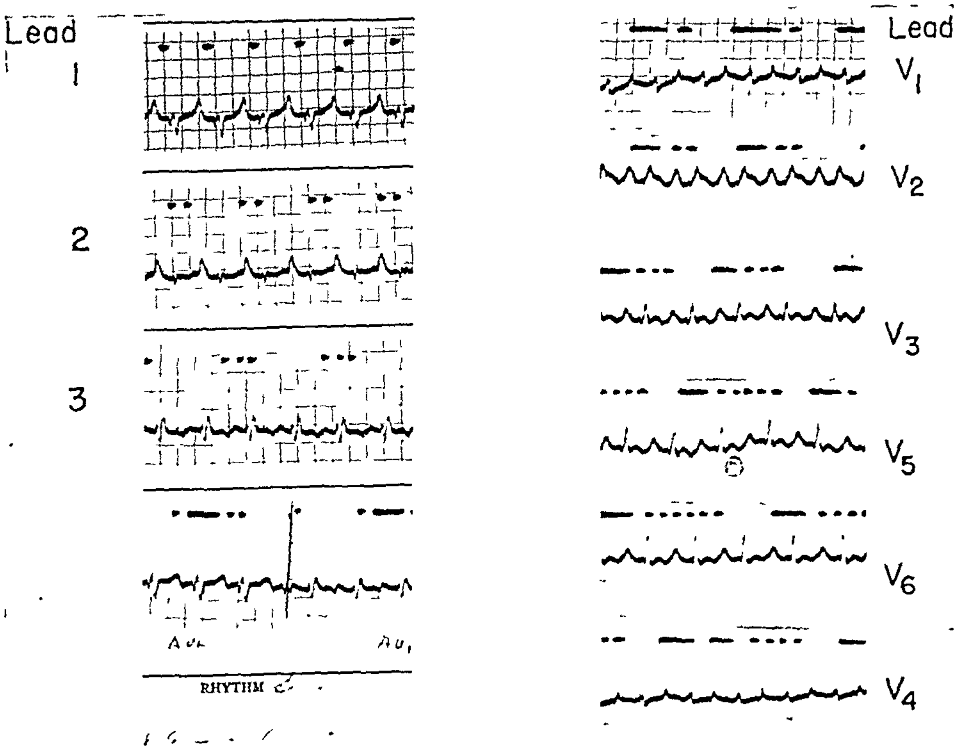
fibrillation. The surgical approach to this congenital malformation has been limited to attempts at closure of the patent foramen ovale or atrial septal defect if such is present. The goal of this palliative procedure is to eliminate the right to left shunt with its resultant desaturation, hematocrit increase, and paradoxic emboli. However, it is probable that the right to left shunt represents a compensatory phenomenon in these patients and its eradication may hasten death by provoking or aggravating right heart failure. In 1956 the Mayo Clinic group reported one survivor out of five cases operated upon by closure of the atrial defect, the other four died soon after surgery or during induction of anesthesia.[3]

It is the purpose of this presentation to offer a more definitive surgical procedure based upon the *in vivo* study of the anatomy in a recently observed case.

Report of Case

The patient was a 10 year old girl who had had cyanosis from birth. Examination and catheterization findings in November of 1952 suggested the diagnosis of Ebstein's malformation. In 1954 the patient was started on digitalis as congestive failure was evident for the first time. Also, at that time it was noted that the hematocrit was increasing. By September of 1955 the hematocrit had reached 66 per cent. In November of 1956 she suffered a left cerebrovascular accident which precipitated the decision to seek surgical treatment

On admission to the University of Minnesota Hospitals for the first time in November 1956, she had right hemiparesis and aphasia. She was deeply cyanotic. Her EKG changes were consistent with the diagnosis of Ebstein's disease with right bundle branch



Peaked P Waves, Prolonged PR Interval, Complete Right Bundle Branch Block.

FIGURE 1

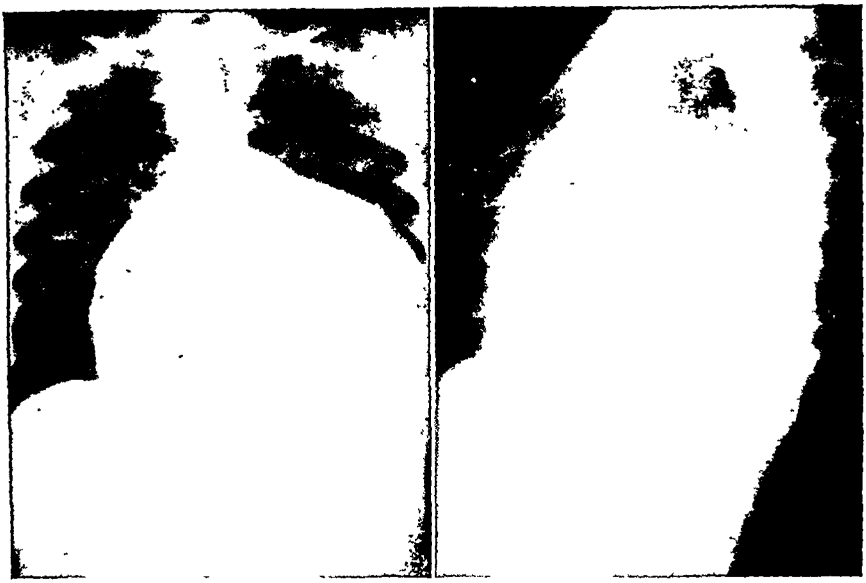


FIGURE 2: Massive cardiomegaly, much enlarged right atrium, large right ventricle, pulmonary artery segment flattened, decreased pulmonary vascularity.

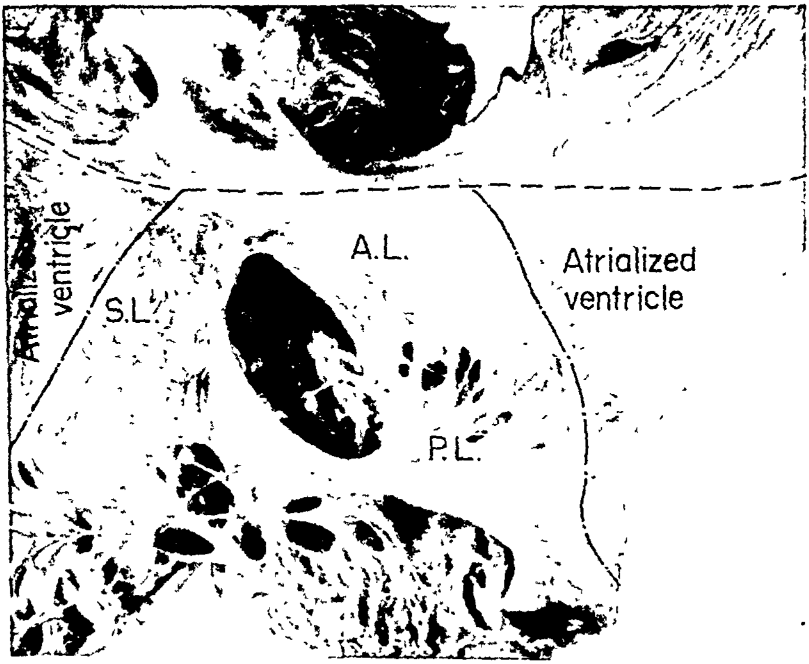


FIGURE 3: View of the displaced Tricuspid valve, note normal position of anterior leaflet, ----denotes true annulus, —.—.—denotes superior border of displaced leaflets. A.L. = anterior leaflet, P.L. = posterior leaflet and S.L. = septal leaflet of Tricuspid valve.

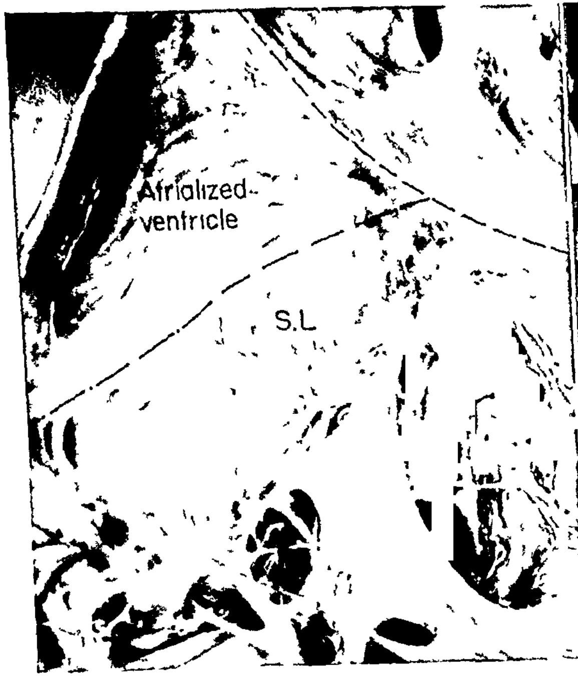


FIGURE 4

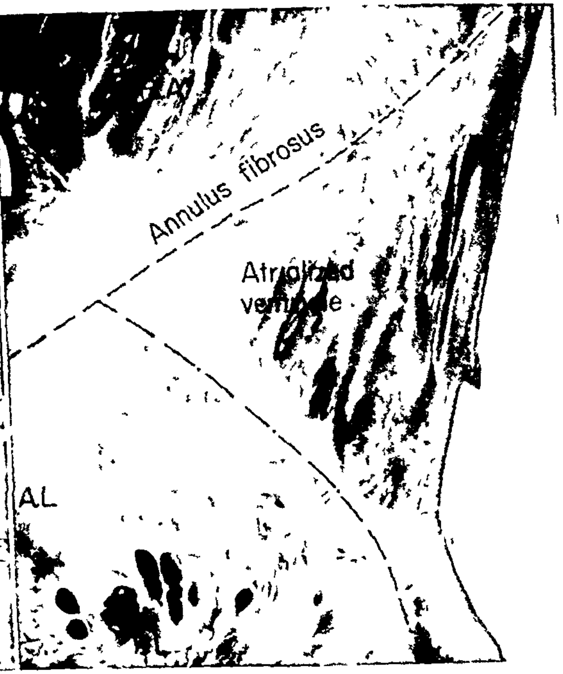


FIGURE 5

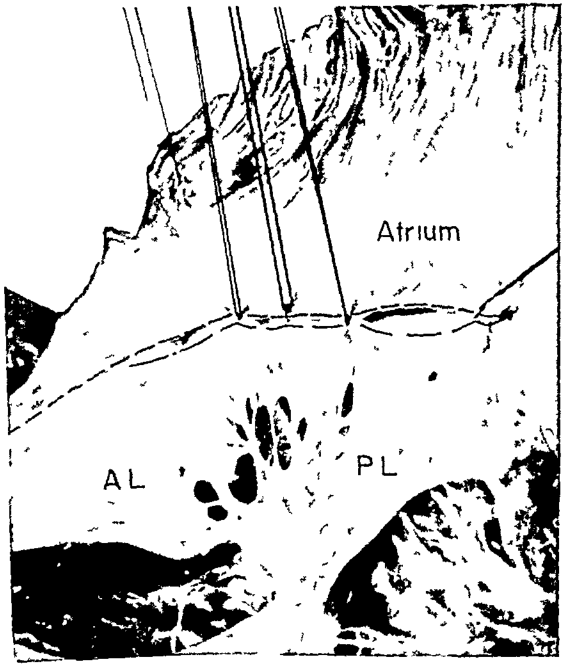


FIGURE 6

Figure 4: Shows the triangular piece of atrialized ventricle between the septal leaflet and the true annulus which is to be excluded. Distortion of septal leaflet is seen.—*Figure 5:* Shows the triangular piece of atrialized ventricular tissue between the posterior leaflet and the true annulus which is to be excluded from heart. R.A. = right atrium, A.L. = anterior leaflet and P.L. = posterior leaflet of tricuspid valve.—*Figure 6:* The superior border of the displaced posterior leaflet has been approximated to the true annulus fibrosis, The triangular area has been excluded by the plicating stitches.

block, peaked P waves, prolonged PR interval (Figure 1). The roentgen picture was also characteristic (Figure 2). A "box-like" appearance of the heart resulting from the narrowed vascular pedicle and enlarged right atrium were prominent features. A few days after admission, thrombophlebitis of the left leg was noted, and anticoagulant therapy was started. Her condition was considered desperate unless something reparative could be done. It was believed unlikely that simple closure of her patent foramen ovale would provide enough therapeutic benefit to make it worth attempting. The proposed alternative was to utilize total cardio-pulmonary bypass with the pump-oxygenator and under direct vision to attempt a reconstruction of the malformed tricuspid valve leaflets together with closure of the patent foramen or atrial defect. It was thought that this could be done by detaching these malpositioned posterior and septal leaflets and reattaching them more normally. After some slight improvement in her condition, this surgery was planned for December 19, 1956; but she expired during induction of anesthesia.

Examination of the fresh specimen in detail revealed an enormously distended right atrium with a paper-thin wall. The heart, principally the right atrium, contained 3000 cc. of blood. The right atrioventricular annulus measured 19 centimeters in circumference as contrasted to 7 centimeters for the left atrioventricular annulus. The leaflet arrangement of the tricuspid valve was similar to the Ebstein original description (Figure 3). The anterior leaflet was for all intents and purposes quite normal in shape and position though considerably larger than normal. The septal and posterior leaflets were displaced into the right ventricle and were attached far below the normal annular location (Figures 4 and 5). There was no atrial septal defect, but a dilated foramen ovale communication was present.

The Suggested Reparative Procedure

Our previous studies upon this malformation has been based, of necessity, upon the rigid, leathery, formalin fixed specimens available from previous years. These are often completely unsatisfactory for purposes of devising surgical treatment as this case illustrates. In studying possible reparative procedures in this pliable specimen it was noted that the malpositioned leaflets could be repositioned more normally by a simpler maneuver than had been planned.

It was possible, in the fresh specimen, and through a right atrial cardiotomy, to place a row of interrupted silk stitches between the true annulus and the false annulus (i.e. the tissue just above the abnormally placed leaflets) (Figures 3 to 5). When tied, these stitches, having been placed with one bite in the true annulus and the other in the false annulus, pulled the posterior leaflet up to the true annulus by plicating outward a fold of the very thin atrialized ventricular wall (Figure 6). The right coronary artery must be safeguarded in the placement of these stitches. As a result of this plication, the triangular shaped piece of ventricular muscle folded outward would no longer function as an integral part of the right atrium. The identical procedure was carried out for the septal leaflet. This plication maneuver would appear simpler, quicker and more feasible than the previously considered procedure of cutting the leaflets free and reattaching them in a more normal position.

The septal portion of this plication operation would perhaps be somewhat more difficult in that there is not the mobility of the septum comparable to the posterior wall of the right ventricle. Nevertheless, it was possible to oppose the annulus fibrous at the septum with the septal leaflet. Moreover, it is proposed that any large and obvious fenestrations in the leaflets themselves should be repaired with fine silk sutures and the atrial defect, if present, closed. As the displaced leaflets were brought up to the annulus in this specimen there was also produced a shortening or snugging up effect upon the annulus, which in this case seemed beneficial. If considerable tricuspid incompetency were still present after plication, the diameter of the atrioventricular ring could be further shortened by placement of a few horizontal mattress stitches tied over small Ivalon pledgets, such as has been utilized for the correction of mitral insufficiency.

One is of course disturbed by the paucity of valve tissue present in the small nubbin-like septal leaflet, but it seemed quite likely that the other two leaflets with their more abundant leaflet tissue should be adequate to complete the atrioventricular closure during ventricular systole, particularly since the anterior leaflet in this specimen had undergone compensatory enlargement. In summary, the multiple potential accomplishments of this plication operation proposed for Ebstein's malformation would be neutralization of the contrary acting ventricular tissue in the atrium, the reduction in annular circumference, and repositioning of the malposed tricuspid leaflets so that they could function more effectively.

Discussion

The right side of the Ebstein heart beats inefficiently and often paradoxically and this surgical procedure should correct these abnormalities. That is, as the right atrium of the Ebstein heart contracts in systole, the ventricular portion which has been atrialized, relaxes in diastole, and when the right atrium is in diastole, the atrialized ventricular portion is contracting. Since these two triangular shaped areas of the atrialized ventricle would be excluded by the plication with stitches as described, the Ebstein heart might be freed of this paradox and recover some efficiency on this basis alone.

According to Kilby's[3] recent study, approximately one-third of the recorded deaths from Ebstein's malformation were the result of congestive heart failure. Thus, it seems likely that a majority of these patients have congestive heart failure in the terminal stages of their disease. In many Ebstein patients there is no disagreement over the presence of clinically obvious tricuspid insufficiency. However, in other patients this incompetency is not immediately obvious probably being masked by the greatly enlarged and distensible right atrium allowing considerable regurgitation of blood by serving as a reservoir and thus acting as a buffer for the systemic veins and the liver. Also, there is the decompressing effect of a patent foramen ovale which may postpone clinically obvious right heart failure. The proneness of these patients to fatal arrhythmias is more difficult to explain, but it is clear that this complication plays a consistently more important role than in most other forms of congenital heart disease. Moreover, cardiac catheterization in this malformation has been more hazardous because of this danger of a serious arrhythmia. It is hoped that the proposed surgical procedure by establishment of more effective right heart function with consequent reduction in the atrial overdistention present might lessen their susceptibility to these arrhythmias. Lev et al[4] have contributed additional information upon these arrhythmias exhaustively studying a case of Wolf-Parkinson-White Syndrome (short PR interval with a prolonged QRS) in an Ebstein heart. These investigators found an anatomic basis for the arrhythmias occurring in their patient. These abnormalities consisted of a right atrioventricular communication outside the usual conduction system, a communication of the right bundle branch and the right side of the septum, and encasement of the right branch in dense fibroelastic tissue. One gains the impression from their study that these extra-conduction pathways consisting of an intermediary muscle bundle with numerous fasiculi to the right atrial appendage and the parietal wall of the right ventricle are the most important elements in the genesis of these conduction irregularities. This may account for the arrhythmias found in the Ebstein heart and also for the unexplained deaths due to this disease. If so, it is possible that the suggested operative technique might alter beneficially this irregular pathway of conduction by deliberately placing the plicating stitches close enough together so as to interrupt these abnormal atrioventricular pathways.

The proposed operation would necessitate total cardiopulmonary bypass with the pump-oxygenator as previously described.[5, 6, 7] Obviously, a trial in patients who have not reached the terminal stages of myocardial decompensation would offer the best test of this hypothesis.

SUMMARY

A case of Ebstein's malformation of the tricuspid valve has been studied. Because of the relative rarity of this defect and the lack of any adequate medical or surgical treatment, a suggested operation is presented for direct attack upon the deformities. Under direct vision by use of total cardiopulmonary bypass the paradoxically contracting atrialized ventricular tissue would be excluded by plication. At the same time, tricuspid valvular function would be improved by the bringing up of the abnormally placed tricuspid leaflets to their true annulus. Also, any patent foramen ovale or atrial septal defect found present would be closed, and fenestrations in the leaflets of the tricuspid valve repaired by fine stitches. The goal of this proposed operation would be the creation of more effective right heart function.

RESUMEN

Se presenta un caso de malformación de Ebstein de la válvula tricúspide. Debido a la falta de tratamiento médico o quirúrgico adecuado, proponemos una operación para la corrección de esta anamalía. La operación tiene por objeto eliminar funcionalmonte el tejido ventricular situado por arriba de las valvas anormalmente desplazadas de tricúspide, mediante la fijación de su borde de inserción al anillo auriculo-ventricular, utilizando un método a cielo abierto y bajo visión directa con ayuda de circulación extracorporea y exclusión cardio-pulmonar circulatoria temporal. Se piensa que la función de la tricúspide mejoraría de esta manera. Simultaneamente una comunicación interauricular o un orificio de Botal persistente, así como posibles fenestraciones en las valvas de la tricúspide, pordían ser reparados ade-

cuadamente. La meta de la operación seria la creación de un corazón derecho funcionalmente más efectivo.

RESUME

Un cas de malformation d'Ebstein de la Valvule tricuspide a été étudié. A cause de la rareté relative de cette lésion et de l'absence de traitement médical ou chirurgical adéquat, nous avons suggéré une technique corrective. La portion "auricularisée" du ventricule, avec contraction paradoxale, serait exclue vers l'extérieur par plicature, sous vision directe á l'aide de l'appareil coeur-poumon. La fonction de la tricuspide étant améliorée du même coup par l'élévation des feuillets valvulaires au niveau de l'anneau trio-ventriculaire. Les anomalies associées telles que "foramen ovale" ou communication interauriculaire seraient suturées et les orifices dans les feuillets tricuspidiens pourraient être réparés en même temps.

Le but de cette intervention est l'amélioration de la fonction ventriculaire droite.

ZUSAMMENFASSUNG

Ein Fall von Epstein's Missbildung der Valvula Tricuspidalis Wurde beschrieben. Die relative Seltenheit dieses Defects erklart den Mangel an adequater chirurgischer oder interner Behandlung. Ein directer operativer Angriff der Missbildungen durch totale Herz-Lungen Ausschaltung unter Sicht ist hiermit empholen. Das sich paradox, Verhof ahnlich contrahierende Kammer Gewebe wird durch Plikation ausgeschlossen. Zur gleichen Zeit kann durch Hebung der Klappen zu ihrem wahren Ring die Funktion der Valvula Tricuspidalis verbassert werden. Ebenfalls kann ein offener Foramen Ovale oder ein Vorhof Septum Defect geschlossen werden und Fenestrierungen der Tricuspidal Klappen mit feinen Nahten repariert werden. Die Verbesserung der Funktion des rechten Herzens ist das Ziel des vorgeschlagenen chirurgischen Eingriffes.

REFERENCES

1 Ebstein, W.: "Ueber einen sehr seltenen Fall von Insufficiency der Valvula Tricuspidalis, bedengt durch eine angeborene hochgradige Misslrldung derselben," *Arch. f. Anat. Physiology. U. Wissench. Med.*, pp. 238-254, 1866.

2 Yater, W. M and Shapiro, M. J.: "Congenital Displacement of the Tricuspid Valve (Ebstein's Disease). Review and Report of a Case with Electro-Cardiographic Abnormalities and Detailed Histologic Study of the Conduction System," *Ann. Int. Med.*, 11:1043, 1937.

3 Kilby, R., Dushane, J. W., Wood, E. H. and Burchell, H.: "Ebstein's Malformation 'A Clinical and Laboratory Study,'" *Medicine*, 35:161, 1956.

4 Lev, M., Gibson, S. and Miller, R. A.: "'Ebstein's Disease' With Wolf-Parkinson-White Syndrome," *Am. Heart J.*, 49:742, 1955.

5 Lillehei, C. W., DeWall, R. A., Read, R. C., Warden, H. E. and Varco, R. L.: "Direct Vision Intracardiac Surgery in Man Using a Simple Disposable Artificial Oxygenator," *Dis. Chest*, 29:1, 1956

6 DeWall, R. A., Warden, H. E., Read, R. C., Gott, V. L., Ziegler, N. R., Varco, R. L. and Lillehei, C. W.: "A Simple, Expendable, Artificial Oxygenator for Open Heart Surgery," *Surg. Clin. North America*, 36:1025, 1956.

7 DeWall, R. A., Warden, H. E., Varco, R. L. and Lillehei, C. W.: "The Helix Reservoir Pump-Oxygenator," *Surg., Gynec. and Obst.*, 104:699, 1957.

8 Lillehei, C. W., Gott, V. L., DeWall, R. A. and Varco, R. L.: "Surgical Correction of Pure Mitral Insufficiency by Annuloplasty Under Direct Vision," *J. Lancet*, Nov., 1957.

Convulsive Syncope Due to Rapid Ventricular Arrhythmias

GEORGE A. SPIKES, M.D., HERBERT G. LIBERTY, M.D.,
WILLIAM H. YATES, M.D. and HARVEY RENGER, M.D.
Hallettsville, Texas

The clinical manifestations of cerebral anoxia due to failure of left ventricular output are identical, regardless of the cause. Variations in the symptoms and signs of cerebral anoxia are due to differences in duration and intensity of circulatory impairment. Cerebral arteriosclerosis, when present, may exert a profound effect. Thus pallor, faintness, and syncope may occur with asystole of 10 to 15 seconds duration, while with longer attacks cyanosis, convulsions, and stertorous breathing appear. Non-fatal attacks lasting longer than 60 seconds are rare, but do occur.[1]

The names of Morgagni, Adams and Stokes are classically associated with episodes of what Morgagni called "epilepsy with a slow pulse." Gerbezius years earlier had described a patient with intermittent slow pulse, dizziness and slight epileptic attacks. It is interesting to speculate that the carotid sinus may have been hyperactive in Morgagni's patient since he wrote " . . . . . so that we now began to fear, lest the head itself had also contracted the injury, especially as, upon a very quick turn of the head, the epileptic insults recurred, and left a sense of weight with stupidness in the head. . . . ."[2] Many years later vasovagal reflexes were recognized as causes of ventricular diastole producing cerebral anoxia.

More recently[3] identical clinical manifestations have been shown to be due to rapid ventricular arrhythmias which impair left ventricular output. Of 64 cases reported by Parkinson et al.,[4] 13 had ventricular tachycardia or ventricular fibrillation without ventricular standstill, 33 had ventricular standstill alone and 18 had ventricular arrhythmias with periods of ventricular standstill. Between syncopal attacks a majority of those with ventricular arrhythmias had complete heart block, and the others (4 of 31) had partial blocks.

We have recently observed four patients in whom ventricular arrhythmias caused cerebral manifestations. These cases illustrate some of the problems in management of these arrhythmias, especially in the presence of atrio-ventricular block.

Case Reports

Case 1: E. G., a 68 year old white woman was admitted with a history of congestive failure six months previously for which she was digitalized. Her blood pressure was 130/80, and the apical rate was 74/minute and grossly irregular. There was moderate cardiomegaly, but no evidence of failure. The admission electrocardiogram (Figure 1A) showed atrial fibrillation. Maintenance digitalis was continued, and the rhythm converted to sinus with quinidine (Figure 1B). She was maintained on 400 mg. quinidine four times daily at home and did well for 10 days, but then she became angry and fainted. When readmitted, atrial fibrillation was again present and quinidine was increased to 600 mg. four times daily. Tracing two days later (Figure 1C) demonstrated a supraventricular rhythm without conducted P waves at a rate of 50/minute.

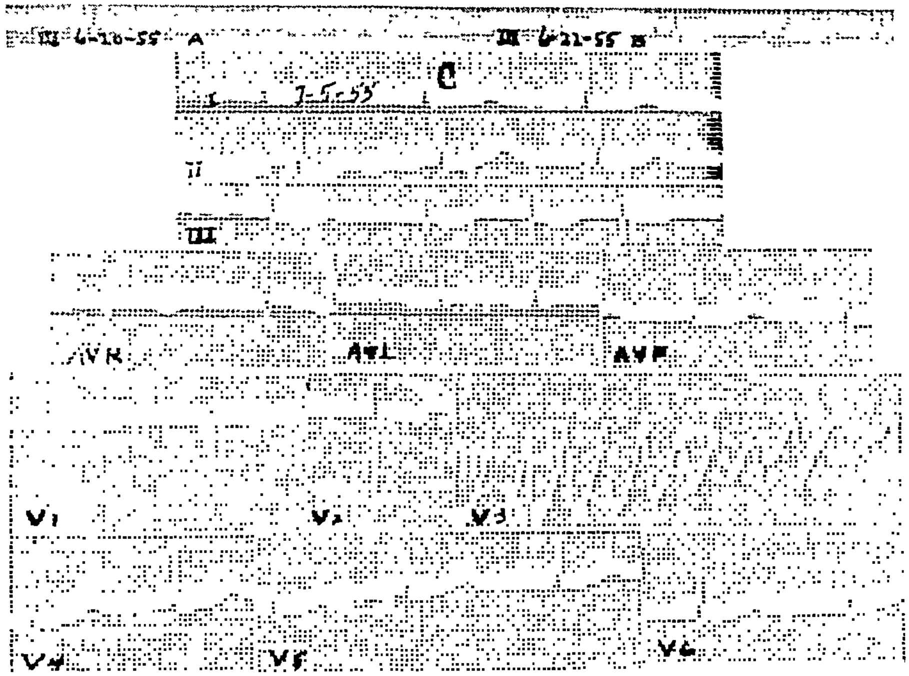


FIGURE 1

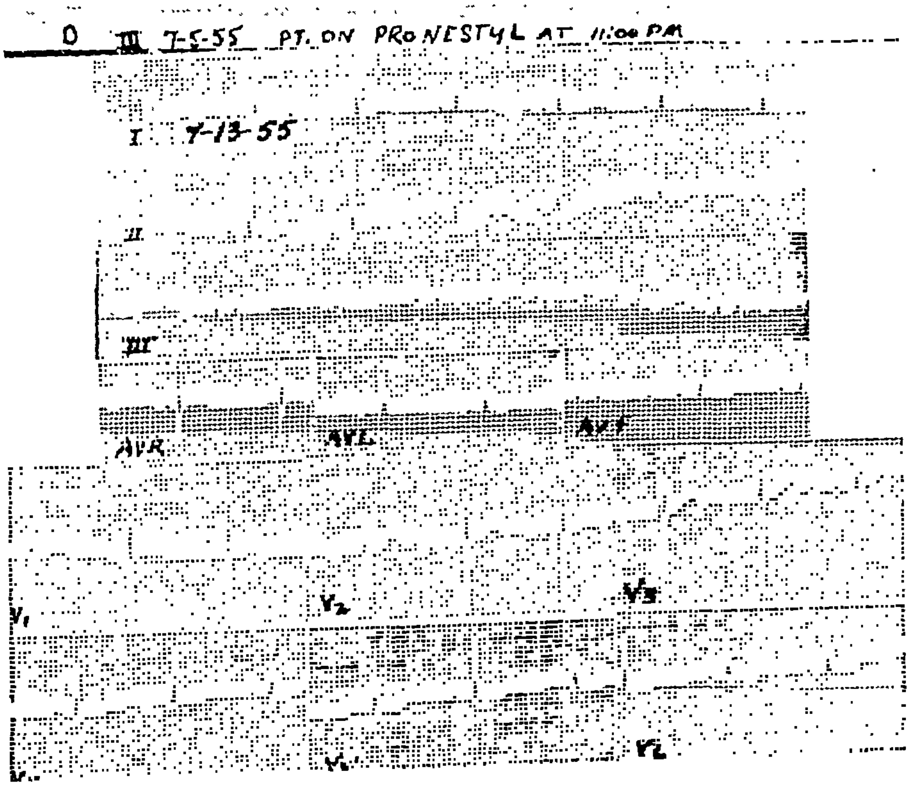


FIGURE 2

Figure 1 (Case 1): This series of electrocardiograms demonstrates toxic effects of quinidine including A-V dissociation, prolonged QT interval and ventricular fibrillation which disappeared when procaine amide was substituted.—*Figure 2* (Case 1): Eight days after an episode of ventricular fibrillation there is no evidence of ventricular hyperirritability.

A ventricular complex arose from the descending limb of T in lead II and the QT intervals were very prolonged (0.64 sec.). While V3 was being recorded she had a syncopal attack identical to the one prior to the second admission. The grossly abnormal rhythm was ventricular fibrillation. Examination revealed absence of pulse and heart tones. The episode lasted only a few seconds. Quinidine was discontinued and procaine amide (Pronestyl) 250 mg. four times daily begun. Sinus rhythm had been restored six hours later (Figure 1D).

A follow-up tracing (Figure 2) eight days later showed sinus rhythm with normal QT intervals and no evidence of excessive ventricular irritability on a dosage of Pronestyl 250 mg. every six hours.

Comment: This case illustrates that quinidine can produce episodes of rapid ventricular arrhythmia. It was shown by Schwartz et al.[5] in 1953 that quinidine produced transient ventricular fibrillation in patients who had conduction disturbances. Because quinidine depresses the inherent rhythmicity and irritability of the heart it is particularly dangerous where there is A-V dissociation. Procaine amide is generally thought to have a similar action, but in this case smaller doses appeared to prevent fibrillations without toxic side effects.

Case 2: W. J., a 62 year old white woman with generalized arteriosclerosis and symptoms of cardiac failure for two months was admitted with a history of increasingly frequent syncopal attacks for one week. Her blood pressure was 190/60, and the apical rate was about 60/minute and irregular. Examination revealed moderate cardiomegaly, reduced peripheral pulses, and evidence of mild right ventricular failure. Admission electrocardiogram showed complete heart block with a regular idioventricular rhythm at a rate of 38/minute. She was given isopropyl norepinephrine (Isuprel) 10 mg. sublingually every four hours, theophylline ethylenediamine (Aminophyllin) 0.5 gm. rectally every eight hours, pentaerythrital tetranitrate (Peritrate) 10 mg. orally every four hours, mercaptomerin (Thiomerin) 1 cc. intramuscularly and epinephrine in oil 0.25 cc. intramuscularly every four hours. Syncopal and convulsive attacks with cyanosis became more frequent. After atropine and meperidine (Demerol) in small doses were given, the electrocardiogram (Figure 3) showed high grade partial A-V block with periods of A-V dissociation and multifocal ventricular premature contractions. Twenty-four hours later she was still having syncopal attacks and an electrocardiogram (Figure 4A and B) showed short paroxysms of ventricular tachycardia at frequent intervals. Finally she was given 100 mg. of procaine amide intravenously over a two minute period. During the injection she had another convulsion. The electrocardiogram (Figure 4C and D) showed runs of ventricular fibrillation and flutter. Pronestyl was discontinued and the last electrocardiogram before death (Figure 4E) taken with the patient conscious, showed complete heart block. Convulsive episodes became more frequent and severe and she expired 12 hours later.

Comment: This case demonstrates the danger of procaine amide in the presence of A-V conduction disturbances. It also shows that convulsive syncope can occur on the basis of ventricular tachycardia and fibrillation. In retrospect there were early clues that the convulsive attacks were not due to ventricular standstill. The obvious hyperirritability of the ventricles evidenced by the multifocal ventricular extrasystoles, and its aggravation by epinephrine was a warning of impending ventricular tachycardia or fibrillation. It is now generally agreed that quinidine and procaine amide are both contraindicated in the presence of conduction defects because they are prone under such circumstances to cause episodes of ventricular fibrillation. The prevention of rapid ventricular arrhythmias is difficult, if not indeed often impossible when complicated by conduction defects. Isopropyl norepinephrine was used in this case but the dosage was small. Results may have been better if subcutaneous or intravenous administration had been possible.

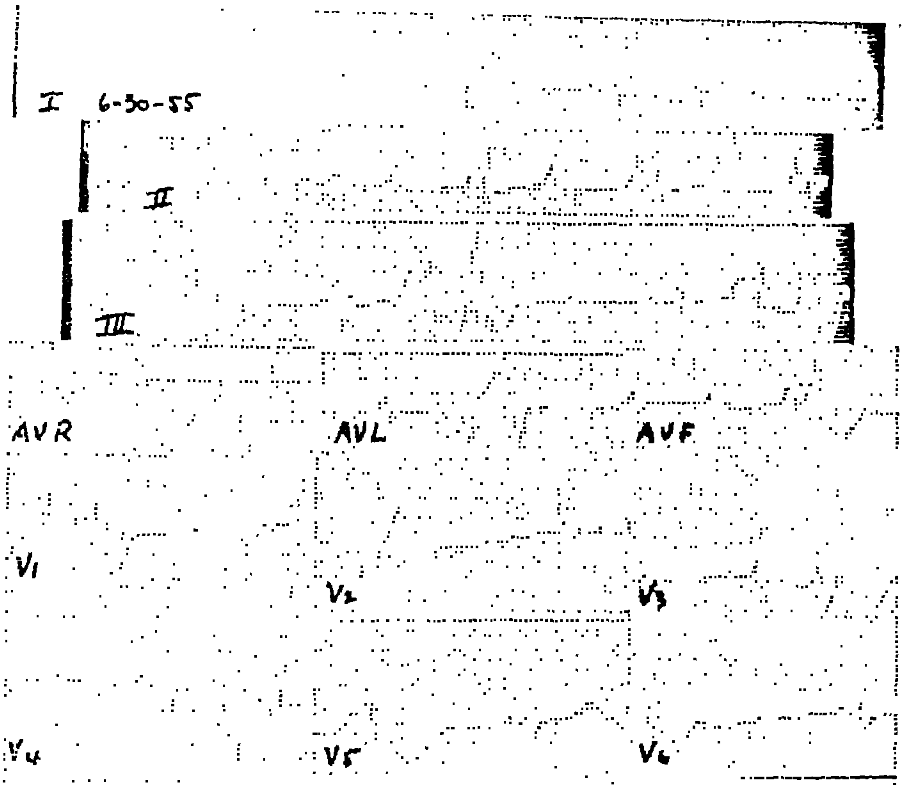


FIGURE 3

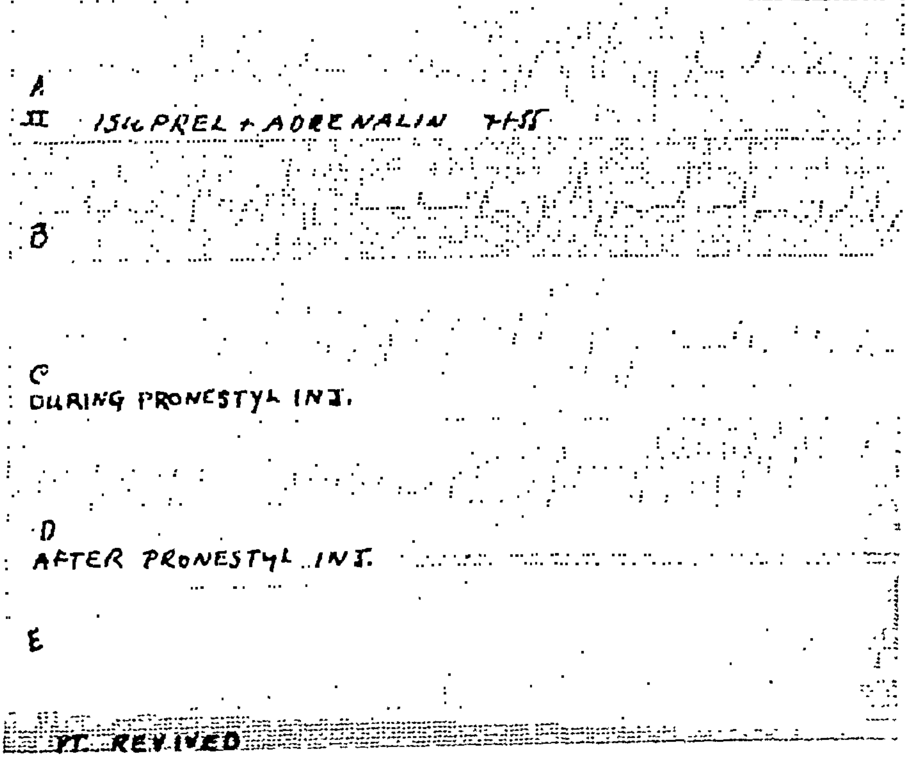


FIGURE 4

Figure 3 (Case 2): This figure demonstrates extreme ventricular hyperirritability in the presence of a high grade partial A-V block.—*Figure 4* (Case 2): The ventricular hyperirritability of the preceding figure has now increased to become runs of prefibrillary tachycardia. Pronestyl at this time caused ventricular fibrillation.

Case 3: J. G., an 81 year old white man was seen in the home because of an episode of syncope. His blood pressure was 200/100, the apical rate 48/minute with regular rhythm. He was given ephedrine and pentobarbital sodium (Nembutal), each 25 mg. every six hours. A second syncopal attack occurred two days later, and he was then admitted in acute severe left ventricular failure. The blood pressure was 240/150, and the apical rate about 40/minute but irregular. Following sedation, an electrocardiogram (Figure 5) showed the termination of an episode of ventricular tachycardia which corresponded clinically with syncope and convulsions. He was given 1.6 mg. lanatoside C (Cedelanid) intravenously but died forty-five minutes after admission.

Comment: This elderly male had advanced arteriosclerotic heart disease. The complete heart block was probably on the basis of fibrosis involving the A-V node or bundle above its bifurcation. The idioventricular rhythm was paced by a focus higher than the bifurcation of the His bundle since the QRS complexes are narrow. An acute infarction probably caused the arrhythmia and acute left ventricular failure, but there were no suporting electrocardiographic signs. Intravenous lanatoside C may have increased the irritability of the ventricles and thus contributed to the final episode of ventricular fibrillation. However, the degree of failure made rapid digitalization imperative.

Case 4: C. B., a 75 year old woman was admitted after having several syncopal attacks in the home and ambulance. She was known to have had long standing arteriosclerotic heart disease, and had been digitalized for years. Each observed episode was similar in that she became apneic, cyanotic, and convulsed. During each attack no heart tones could be heard, and no pulse felt. Between attacks she was conscious, and the apical rate was 92/minute and regular. The episodes occurred at intervals of four to five minutes and lasted 15 to 20 seconds. Procaine amide 200 mg. intravenously was given in the home. Upon admission to the hospital fifteen minutes later an electrocardiogram (Figure 6A) was taken. While ventricular fibrillation was being recorded in V3, she had another episode from which she spontaneously recovered. While the electrodes were still in place she became apneic and pulseless, and was given intracardiac epinephrine. The electrocardiogram (Figure 6B) showed ventricular tachycardia at a rate of 180/minute. During this tracing she again recovered for a few minutes more. However, after being given 200 mg. procaine amide intravenously, she expired five minutes later during another attack.

Comment: The sudden onset of symptoms and the variety of rhythms occurring in a subject with known arteriosclerotic heart disease raises the question of myocardial infarction. There was however no pain, and the electrocardiogram is not diagnostic of acute infarction, although there are evidences of old posterior scarring.

The electrocardiogram (Fig. 6*A*) shows A-V dissociation with a faster atrial (110/minute) than ventricular (100/minute) rate in the standard leads. Ventricular prematures are present singly in leads II, III and AVR and in runs in V2. Ventricular fibrillation is seen in V3 and a supraventricular tachycardia at a rate of 150/minute is seen in V4, V5 and V6. In view of the known propensity of procaine amide to cause ventricular arrhythmias in complete heart block[6] the possibility that some of these arrhythmias were due to that drug cannot be denied. The last electrocardiogram taken five minutes before death shows typical ventricular tachycardia at 180/minute. Heart tones and peripheral pulses were present and she was conscious during this time.

Discussion

Ventricular asystole is classically considered due to ventricular standstill, which can be due either to extreme ventricular bradycardia in or-

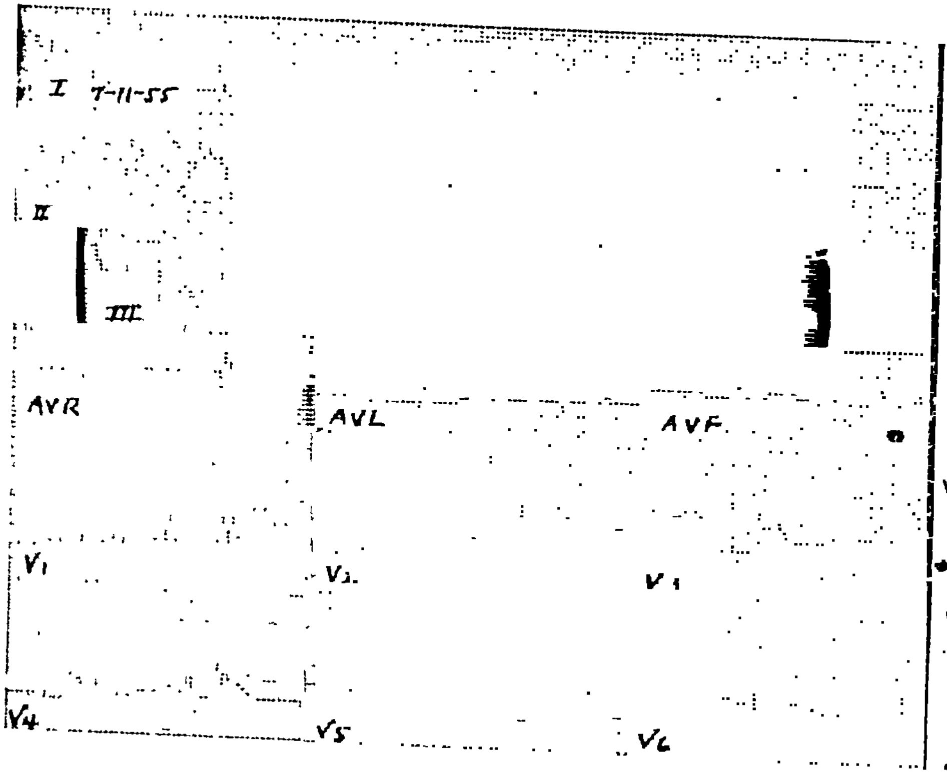


FIGURE 5

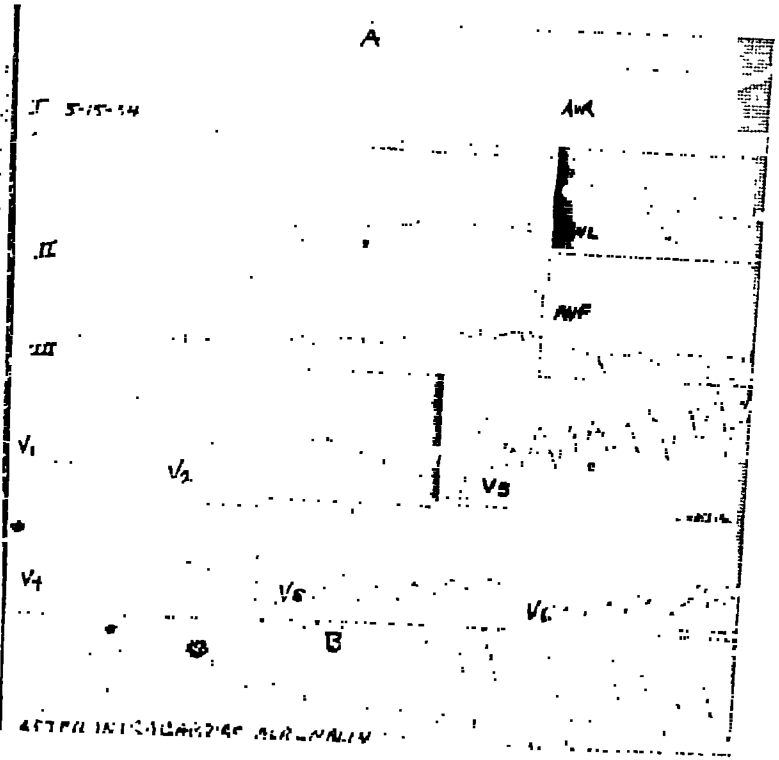


FIGURE 6

Figure 5 (Case 3): Complete A-V dissociation in a patient with severe pulmonary edema and syncope with convulsions due to ventricular tachycardia.—*Figure 6* (Case 4): The patient was unconscious and without pulse or heart tones during the tracing of V3. Strip B was made when heart tones and pulse were present, and the patient was conscious.

ganic A-V block or to excess vagal tone in carotid sinus syncope. The block may be due to depression of the conduction mechanism by excess vagus tone or to disease within the conduction system itself, especially fibrosis and anoxia, but sometimes inflammation. Clinically indistinguishable episodes accounting for about one-half of cases of convulsive syncope may however be due to ventricular asystole caused by one of the rapid ventricular arrhythmias. A clinical clue may sometimes be found in palpitation felt by the patient or in recognizing frequent premature beats, but electrocardiographic study is necessary in every case and is the only reliable method by which ventricular standstill and ventricular fibrillation can be distinguished. It is important to make this distinction since logical treatment depends upon accurate diagnosis.[7] It is helpful to think of asystole as being due to a myocardium that is either not irritable enough, as in some cases of A-V block, or too irritable, as in the case of a rapid ventricular arrhythmia.

Rational treatment follows from understanding the mechanism which is causing the attack. Vasovagal syncope is usually effectively treated with atropine or methantheline (Banthine).[8] Surgical denervation of the implicated carotid sinus may be curative, but is rarely necessary.

When the myocardium is not irritable enough and ventricular standstill is causing the attacks, myocardial stimulants are indicated. Epinephrine is classically the drug of choice, usually administered in oil. Because of its ability to cause ventricular arrhythmias it should be used cautiously and only after the syncopal mechanism is known. Barium chloride increases ventricular irritability, but predisposes to ventricular fibrillation and is now rarely used. Ephedrine is similar to epinephrine and can be given orally. All these drugs are contraindicated in cases of rapid ventricular arrhythmias. Standstill and arrhythmias may be found in the same patient at different times. This complicates treatment since the danger of epinephrine producing ventricular fibrillation or perpetuating it is greater than the danger from transient ventricular arrest.

Quinidine and procaine amide are considered drugs of choice in terminating uncomplicated ventricular arrhythmias when heart block, bundle branch block and intraventricular block are absent. In the presence of these frequent complications however, both drugs have the capacity to cause or perpetuate rapid ventricular arrhythmias. If given intravenously, continuous electrocardiographic monitoring is essential.

Schumacher et al.[9] found isopropyl norepinephrine (Isuprel) to be the drug of choice in convulsive syncope. Whereas epinephrine predisposes the heart to ventricular fibrillation, Isuprel stimulates the higher pacemakers without increasing ventricular irritability. By keeping a higher (more rapid) pacemaker active, the ventricular refractory period is prolonged and fibrillation prevented. Isuprel has no effect on junctional tissue, as have quinidine and procaine amide. Having little pressor activity, it is not contraindicated by the presence of hypertension. Isuprel may be administered sublingually in doses of 10 mg. as often as is necessary to prevent attacks. Parenteral dosage forms of the drug are also available

If used subcutaneously 0.2 mg. as often as every hour may be used. Intravenously, 1 mg. in 200 cc. of 5 per cent glucose may be given at a rate of 10-20 drops per minute as indicated by electrocardiographic monitoring. The value of Isuprel in convulsive syncope complicating heart block is confirmed in a series reported by Wright et al.[10]

Recently[11] a patient with heart block of suspected inflammatory etiology was helped by the use of the anti-inflammatory action of corticotropin (ACTH).

Sodium lactate has been reported[12] of value in cases of ventricular arrest when not due to excess vagal tone. The mode of action is unknown. The possibility of precipitating conjestive failure with large amounts of sodium must be considered.

Electrical stimulation[13] of the heart has proved life saving both in instances of ventricular standstill and in ventricular fibrillation. The value of cardiac massage and electric defibrillation is well known. Supportive measures would include the use of oxygen as arterial oxygen saturation should be raised to as near a normal level as possible. Measures aimed at increasing the coronary blood flow may help to carry the oxygenated blood to the hypoxic conduction system, and thus one or several of the commonly used coronary vasodilators appear worthwhile.

SUMMARY

1. Convulsive syncope due to cerebral anoxia as a result of decreased left ventricular output occurs in ventricular standstill and in rapid ventricular arrhythmias such as tachycardia and fibrillation. Cerebral arteriosclerosis profoundly influences the overall picture.

2. Electrocardiographic study is essential prior to definitive treatment since this is the only certain method by which a distinction can be made between standstill and arrhythmia. Standstill and arrhythmia may occur in the same patient at different times.

3. Myocardial infarction not infrequently causes ventricular arrhythmias.

4. General measures applicable to most patients include oxygen, coronary vasodilators and rest.

5. Uncomplicated ventricular standstill may be treated with epinephrine, but the drug is contraindicated in arrhythmias.

6. Ventricular arrhythmias in the absence of conduction defects may be treated with quinidine or procaine amide. These agents are absolutely contraindicated in the presence of conduction defects because of their tendency to produce ventricular arrhythmias.

7. Isopropyl norepinephrine (Isuprel) is the drug of choice in convulsive syncope. It is not contraindicated in infarctions, hypertension, conduction defects or arrhythmias.

RESUMEN

1. El síncope convulsivo debido a anoxia cerebral acontece como un resultado del rendimiento ventricular izquierdo disminuido en el paro ven-

tricular y en arritmias ventriculares rápidas tales como taquicardia y fibrilación. La arterioesclerosis cerebral influye profundamente en el cuadro general.

2. El estudio electrocardiográfico es esencial antes del tratamiento definitivo puesto que es el único método cierto por que puede distinguirse entre paro y arritmia. El paro y la arritmia pueden ocurrir en el mismo enfermo en tiempos diferentes.

3. El infarto del miocardio no es poco frecuente que cause arritmias ventriculares.

4. Las medidas generales aplicables a la mayoría de los enfermos comprenden: oxígeno, vasodilatadores coronarios y reposo.

5. El paro ventricular no complicado puede tratarse con epinefrina, pero la droga está contraindicada en las arritmias.

6. Las arritmias ventriculares en ausencia de defectos de conducción pueden tratarse con quinidina o amida-procaína. Estos medicamentos están absolutamente contraindicados en presencia de defectos de conducción por su tendencia a producir arritmias ventriculares.

7. En el síncope convulsivo la droga de elección es el isopropil norpinefrina (Isuprel). No está contraindicado en los infartos, en la hipertensión, los defectos de conducción o arritmias.

RESUME

1. Une syncope convulsive due à l'anoxie cérébrale par suite de la diminution du débit ventriculaire gauche peut survenir en cas de pause ventriculaire et dans les arythmies ventriculaires rapides, telles que tachycardie et fibrillation. L'artériosclérose cérébrale joue un rôle important dans le tableau.

2. Une étude électrocardiographique est essentielle avant d'instituer un traitement définitif, puisque c'est le seul moyen certain de pouvoir faire la distinction entre pause ventriculaire et arythmie. La pause et l'arythmie peuvent survenir chez le même malade à des moments différents.

3. Il n'est pas rare que l'infarctus myocardique soit à l'origine d'arythmies ventriculaires.

4. Les mesures générales applicables à la plupart des malades comprennent l'administration d'oxygène, les vasodilatateurs des coronaires, et le repos.

5. Une pause ventriculaire sans complication peut être traitée par l'épinéphrine, mais le produit est contre-indiqué dans l'arythmie.

6. L'arythmie ventriculaire, en l'absence de défauts de conduction, peut être traitée par la quinidine ou l'amide procaïnique. Ces produits sont absolument contre-indiqués en cas de malformations car ils ont tendance alors à être cause d'arythmie ventriculaire.

7. La "norepinephrine isopropyle" (Isuprel) est la médication de choix dans la syncope convulsive. Elle n'est pas contre-indiquée en cas d'infarctus, d'hypertension, de défauts de conduction ou d'arythmies.

ZUSAMMENFASSUNG

1. Kollaps mit Krämpfen infolge cerebraler Anoxie als Folge eines herabgesetzten Schlagvolumens des linken Ventrikels kommt vor bei Herzstillstand, sowie bei rasch folgenden ventrikulären Arrhytmien wie z.B. Tachycardie und Kammerflimmern. Eine cerebrale Arteriosklerose beeinflusst in erheblichem Grade das Gesamtbild.

2. Elekktrocardiographische Untersuchung ist wesentlich vor endgültiger Behandlung, das dies die einzig sichere Methode ist, mit daren Hilfe eine Unterscheidung getroffen werden kann zwischen Stillstand unr Arrhytmie. Stillstand und Arrhytmie können zu verschiedenen Zeiten bei demselben Kranken vorkommen.

3. Myocard-Infarktbildung bedingt nicht selten ventrikuläre Arrytmien.

4. Allgemeine Massnahmen, die bei den meisten Patienten anwendbar sind, umfassen Sauerstoff, coronare Vasodilatatoren und Ruhe.

5. Nicht komplizierter ventrikulärer Herzstillstand lässt sich mit Epinephrin behandeln, jedoch ist dieses Mittel bei Arrhytmien contraindiziert.

6. Ventrikuläre Arrhytmien beim Fehlen von Reizleitungsstörungen können mit Quinidin oder Procain-Amid behandelt werden. Diese Stoffe sind völlig contrindiziert beim Bestehen von Reizleitungs-störungen wegen ihrer Tendenz, ventrikuläre Arrhytmien hervorzurufen.

7. Isopropyl-Norepinephrin (Isuprel) ist das Mittel der Wahl bei Kollaps mit Krämpfen. Es ist nicht contraindiziert bei Infarkten, Bluthochdruck, Reizleitungsstörungen oder Arrhytmien.

REFERENCES

1 Friedberg, C. K.: *Diseases of the Heart.* Philadelphia, 1956. W. B. Saunders Co.

2 Major, R. H.: *Classic Descriptions of Disease.* Springfield, 1945. Charles C Thomas.

3 Pastor, B. H. and Worrilow, S. H.: "Electrocardiographic Patterns in Stokes-Adams Syndrome," *Ann. Int. Med.*, 34:80, 1951.

4 Parkinson, J., Papp, C. and Evans, W.: "The Electrocardiogram of the Stokes-Adams Attack," *Brit. Heart J.*, 3:171, 1941.

5 Schwartz, S. P., Margolies, M. P. and Firenze, A.: "Transient Ventricular Fibrillation V. The Effects of the Oral Administration of Quinidine Sulfate on Patients with Transient Ventricular Fibrillation During Established Atrioventricular Dissociation," *Am. Heart J.*, 45:404, 1953.

6 Schwartz, S. P., Hallinger, L. and Imperialli, A.: "Transient Ventricular Fibrillation IV. The Effects of Procaine Amide on Patients with Transient Ventricular Fibrillation During Established Auriculoventricular Dissociation," *Circulation*, 6:193, 1952.

7 Robbin, S. R., Goldfein, S., Schwartz, M. J. and Dack, S.: "Adams-Stokes Syndrome: The Treatment of Ventricular Fibrillation Associated with Complete Heart Block," *Am. J. Med.*, 18:577, 1955.

8 Haymond, T. and Bellet, S.: "Effect of Banthine on the Cardiac Mechanism in States Associated with Increased Vagal Tone," *Am. J. Med.*, 16:516, 1954.

9 Schumacher, E. E., Jr., and Schmock, C. L.: "Control of Certain Cardiac Arrhythmias with Isopropyl-Nor-Epinephrine (IPN)," *Am. Heart J.*, 48:933, 1954.

10 Wright, J. C., Hejtmancik, M. R., Herrmann, G. R. and Shields, A. H.: "A Clinical Study of Complete Heart Block," *Am. Heart J.*, 52:369, 1956.

11 Prinzmetal, M. and Kennamer, R.: "Emergency Treatment of Cardiac Arrhythmias," *J.A.M.A.*, 154:1049, 1954.

12 Bellet, B., Wasserman, F. and Brody, J. I.: "Treatment of Cardiac Arrest and Slow Ventricular Rates in Complete A-V Heart Block: Use of Molar and Half Molar Sodium Lactate-Clinical Study," *Circulation*, 11:685, 1955.

13 Zoll, P. M. Linenthal, A. J., Blegard, A. H. and Norman, L. R.: "Treatment of Stokes-Adams Disease by External Electric Stimulation of the Heart," *Circulation*, 9:482, 1954.

CURRENT THERAPY

The Editorial Board invites your comment.

Treatment of Peripheral Arterial Disease

The purpose of the present report is to review briefly the effective therapeutic procedures and drugs which are being employed currently for the treatment of the peripheral arterial diseases. The treatment of diseases of veins, capillaries and lymphatics will not be discussed. The treatment of the arterial diseases is medical and surgical.

Medical Treatment

Medical treatment consists of 1) protective measures, 2) drugs and 3) physical therapeutic procedures.

Protective Measures:

The patient should: 1) stop smoking, unless he has had a successful sympathectomy, in which case smoking no longer decreases blood flow in the sympathectomized area, 2) walk only to the point of pain, 3) dress warmly, 4) elevate the head of the bed, 5) avoid the foot-up position, 6) not apply heat directly to the feet, 7) not soak the feet in water for long periods unless directed by a physician and 8) use alcohol freely in the form of whiskey if there are no contra-indications.

Drugs:

The agents useful for the treatment of peripheral vascular disease fall into at least the following categories: 1) locally acting agents, 2) systemic antibacterial agents, 3) anticoagulants, 4) muscle depressants, 5) adrenal steroids, 6) vasodilators, 7) vascoconstrictors, 8) positive inotropic agents, 9) vitamins and 10) anticholesteremic agents.

Locally acting agents: These are the fungicides, bacteriostatic, cleansing and proteolytic agents.

Fungicides: Athelete's foot may be kept under control with propionate-caprylate (Sopronol®) powder or ointment, or if this fails potassium permanganate soaks 1:10,000 may be employed.

Bacteriostatic agents: Necrotic tissue should be removed mechanically or by soaks with cleansing or proteolytic agents after which cultures are made to identify the infecting organism. Gram positive organisms often are sensitive to penicillin, 1,000 units aqueous per cc., or to bacitracin in the same dosage. Gram positive mixed with gram negative organisms may be treated with Sulfamylon® 5 per cent and streptomycin 200 units per cc. Pseudomonas aerugonosa and pyocyaneous organisms respond to Aureomycin® ointment 3 per cent or a polymyxin bacitracin mixture (Polycin®) 1 per cent ointment.

Cleansing agents: Aluminum subacetate 0.5 per cent solution in distilled water helps to remove crusts and stop itching.

Proteolytic agents: These remove fibrin and cellular debris. Varidase®

or Tryptar® may be employed. Varidase® is a mixture of streptokinase and streptodornase which are agents excreted by the streptococci. They split fibrin into polypeptides thereby dissolving exudates. Tryptar® is trypsin, a crystilline material from the pancreas which digests non-viable cells but does not attack living cells.

Systemic antibacterial agents: When fever is present cultures from ulcers may suggest the offending organism. Sensitivity tests dictate the type of drug to be used. The gram positive organisms generally respond to penicillin. Gram negative organisms respond to streptomycin. When the organism is unknown a combination of penicillin and streptomycin intramuscularly gives a broad spectrum of antibacterial activity. A wide spectrum of antibacterial action is obtained with oxytetracycline (Terramycin®) orally.

Anticoagulants: These are used for the prophylaxis of arterial thrombosis or embolus, in patients with atrial fibrillation or mural thrombosis, after trauma to vessels from frostbite and after crush injuries. They are contraindicated in patients with abnormalities of the clotting mechanism, liver disease, late pregnancy, advanced renal disease, recent peptic ulcers, subacute bacterial endocarditis, necrotizing arteriolitis, aneurysms of the aorta or when reliable prothrombin and coagulation tests are not available.

Types of drugs: These are heparin which alters the coagulation time and the coumarin and indandione derivatives which alter the prothrombin time.

Heparin: When a rapid onset of action and a short duration is desired heparin is given six times daily intravenously or intramuscularly. When a longer effect is desired it is given deeply subcutaneously every 12 hours using a highly concentrated solution of 200 mg. per cc. Regardless of the method of administration the total dose in 24 hours is based on body weight. For a 100 pound subject 200 mg., 150 pound subject 250 mg. and a 200 pound subject 300 mg. is administered. Coagulation times are taken every 24 hours just before an injection and should be about 2 times normal or about 20 minutes.

Coumarin and indandione derivatives: These agents are employed for intermediate or long term anticoagulant therapy and are listed in Table I. There are some differences between these agents which involve the size of the effective dose, the time of onset of action, the duration of the effect, the time required for the prothrombin time to return to normal after the drug has been stopped, and the effectiveness of vitamin K as an antidote. Acenocoumarin (Sintrom®) has the advantage of a small oral and maintenance dose with rapid onset of action with moderate duration of effect. Diphenadione (Dipaxin®) has a small initial and maintenance dose with a slower onset of action and longer duration than Sintrom®. Warfarin (Coumadin®) has the advantage of an intravenous route of administration which prevents variations in effect due to absorption, with rapid onset of action. The antidote for all of these agents is fresh transfusions, vitamin K_1 (Mephyton®) orally and parenterally.

Vitamin K is not effective against cyclocoumarol (Cumopyran®) or phenandione (Danilone®).

Muscle depressants: These are effective for most night cramps regardless of their etiology. Quinidine sulfate 0.2 gram or quinine 0.6 gram with Benadryl 50.0 mg. before bed are effective.

Adrenal Steroids: Prednisone (Meticorten®) 30.0 mg. daily, Prednisolone (Meticortelone®) 30.0 mg. daily or ACTH, 40.0 mg. daily are employed in the treatment of periarteritis nodosa and disseminated lupus erythematosus. They are only slightly effective against scleroderma. Prednisone and prednisolone have very little tendency to cause sodium retention and potassium excretion. ACTH is generally used to stimulate the adrenal gland after prednisone and prednisolone have been employed for some time.

Vasodilator drugs: These agents for greatest effectiveness should be employed in combination.

Meprobamate (Equanil®), 400 mg. 3 times a day, is employed to prevent central stimulation of the vasomotor center when vasoconstriction is functional.

The DH alkaloids of ergot (Hydergine®), 0.5 mg. 4 times a day sublingually or 0.25 mg. subcutaneously or intramuscularly, depress the vaso-

TABLE I

Drug	Initial Dose Mg.	Maintenance Dose Mg./Day	Time of Onset of Action-Hrs.	Peak Effect Days	Recovery of Prothrombin or Coagulation Time After Stopping Drug—Days	Antidote
Heparin	75 mg. IVI 100 mg. SC	200 SC	¼	1 hr.	3 hrs. after IV 12 hrs. after SC	Protamine Sulfate Transfusion Toluidine blue
Dicoumarol Dicumarol®	1st day 300 2nd day 200	50-100	36	3	5	Vitamin K_1 or K Transfusion
Ethyl biscoumacetate Tromexan®	1500-1800 divided	600-900 divided	18	1	2	Vitamin K_1 or K Transfusion
Warfarin Coumadin®	65 IVI 85 oral	12.5 oral	24 oral 12-24 IVI	2 oral	4	Vitamin K_1 or K Transfusion
Cyclocoumarol Cumopyran®	1st day 100-200 2nd day 75	12.5-50	24	2	5	Vitamin K_1 Transfusion (K not effective)
Phenindione Danilone®	200-300	25-100	18	2	3	Vitamin K_1 Transfusion (K not effective)
Diphenadione Dipaxin®	1st day 20-30 2nd day 10-15	3-5	48	3	7	Vitamin K_1 or K Transfusion
Acenocoumarin Sintrom®	20 oral	8-12	24	1 and ½ to 2	2-3	Vitamin K_1 or K Transfusion

motor center in the hypothalomus and have a slight sedative and adrenolytic effect which is useful for patients with Raynaud's disease when the upper extremities are involved.

Chlorisondamine (Ecolid®), a ganglionic blocker is useful for the diagnosis of causalgia but is not generally employed for prolonged treatment.

Phenoxybenzamine (Dibenzyline®), 10.0 mg. 3 times a day, is a useful adrenolytic agent which blocks the sympathetic nerve endings and produces vasodilatation in patients with arteriosclerosis obliterans or Buerger's disease.

Three pyridine-methanol (Roniacol®) if given in sufficient doses is a useful vasodilator and has a direct action on the blood vessel wall. A minimum of 100 mg. 4 times a day is given. It is more effective when the Timespan tablet is employed in doses up to 900 mg. daily.

Vasoconstrictor Drugs: Cigarette smoking, ergotamine tartrate (Cafergot®) and ephedrine are employed in erythermalgia.

Positive inotropic agents: Norsuprifen (Arliden®) is a positive inotropic agent which increases the force of the cardiac contraction and increases muscle circulation and is employed for intermittent claudication. The dose is 6.0 mg. three times daily.

Vitamins: VitaminB_{12}, 100 mcg. daily parenterally, is employed for diabetic neuritis and if this provides relief of pain, the agent may be tried orally but is less effective by this route.

Anticholesteremic agents: Although the exact relationship of the blood cholesterol to arteriosclerosis is not known, it seems wise to normalize the cholesterol when it is abnormal. The underlying causes such as diabetes, hypothyroidism and nephrosis should be corrected when possible. When the cause of an elevated cholesterol is not known the following may be employed.

Thyroid preparations: Triiodothyronine (Cytomel®) in doses of 25.0 to 50.0 mcg. daily lowers the cholesterol but should not be given in patients with coronary artery disease as angina may be precipitated. Other thyroid preparations are effective also but with Cytomel the cholesterol level stays down better when it is continued for long periods of time than with some other preparations.

Beta sitosterol: (Cytellin®), one or two tablespoonsful 3 times a day, is certainly effective in many patients as it prevents the absorption of cholesterol in the food. This can be shown clearly with appropriate fat tolerance tests.

Safflower oil: (Saff®) also is effective in a significant number of patients. The dose is one ounce twice daily. It is postulated that the high linoleic acid content is responsible for its cholesterol lowering property.

Estrogens: These lower cholesterol, however, undesirable side effects are produced. New estrogens under clinical investigation may be without these side effects.

Physical Therapeutic Procedures:

Indirect body heating: Moderate heat to the trunk increases the circulation to the limbs. If the heat is excessive the blood in the diseased limb will be directed away from the diseased areas to the more healthy areas. Thus, this procedure should be used cautiously.

Oscillating bed: This is useful in some patients with ulceration of the skin when there is a tendency for swelling to occur. By adjusting the bed with the maximum foot-down and minimum foot-up position throughout its cycle, the arterial circulation to the feet is increased with minimal edema because venous dumping occurs periodically. Vasodilators should be used simultaneously with this treatment.

Leg cradles: These are used without heat or with a 25 watt bulb merely to maintain the skin at normal temperature under the cradle. When the lamp is not employed the legs should be wrapped in stockinette to prevent heat loss from evaporation.

Surgical Treatment

Surgical treatment includes sympathectomy, arterial grafts, vein grafts, plastic prostheses, embolectomy, thromboendarterectomy, arterectomy, arterial shunts and amputation.

Sympathectomy: This increases the circulation to the arms and hands and to the distal thirds of the legs and feet. The procedure is used when disease of small vessels is present (diabetes) or when it is impractical to restore the patency of large arteries by graft or other direct methods. The major indication for sympathectomy is the presence of an increased sympathetic vasoconstrictor tone which is suggested by a history of cold feet during the day with warming of the feet at night, or by cold wet feet and constricted veins which become warm and pink after a diagnostic posterior tibial nerve block which can be carried out as an office procedure. The diseases improved by sympathectomy are arteriosclerosis obliterans, Buerger's disease, diabetes, sympathetic dystrophy, Raynaud's disease and acrocyanosis. The selection of patients for sympathectomy is facilitated by plethysmographic tests.

Arterial grafts: Arterial homografts have been successful for repairing weakened or dilated vessels, to restore patency to obstructed arteries and for temporary or permanent shunts to bypass obstructions in an artery. The homograft is indicated for replacing aneurysms of the abdominal aorta, popliteal arteries, and for the repair of chronic obstruction of large arteries such as the aorta, iliac, femoral and popliteal arteries.

Vein grafts: These are generally less satisfactory than arterial grafts because they tend to dilate and calcify.

Plastic prostheses: Vinyon N, Nylon, Dacron and Teflon have all been employed. Generally arterial homografts are somewhat easier to handle than are the plastic prostheses, although the prostheses have the advantage of ready availability.

Embolectomy: This is indicated usually when an embolus has been present for only a few hours because after this time proximal or distal thrombosis of the artery occurs. As soon as the embolus is recognized heparin is given intravenously every four hours up to the time of surgery at which time protamine sulfate may be given to stop its effects. Embolectomy usually is carried out when the embolus is lodged in the aorta, iliac, femoral or popliteal arteries. After surgery heparin and dicoumarol are given continuously. The heparin is stopped in a few days and the dicoumarol is stopped in a few weeks.

Thromboendarterectomy: This procedure involves the removal of obstructing material from within the artery, and is indicated when large arteries, such as the iliac and femoral arteries, are obstructed for short distances and the distal arteries are patent. This procedure has the advantage that dilatation of the weakened vessel may occur postoperatively.

Arterectomy: The removal of an obstructed arterial segment was advocated by Leriche who thought that surgery removed an irritating focus which produced vasoconstriction. This procedure is not advisable if an arterial homograft can be carried out.

Arterial shunts: These may be temporary or permanent and consist of arterial homografts which pass around the obstruction. These have been used to bypass obstructions in the superficial femoral artery, the bypass extending from the common femoral artery to the popliteal. There is a slight tendency for these grafts to thrombose after months or years.

Amputation: As a last resort amputation may be necessary. Amputation should be carried out at the lowest possible site.

Other methods of treatment: Peripheral nerve crush is not generally successful because of the adrenalin sensitivity which develops with resultant vasoconstriction. Intra-arterial therapy with Priscoline® and other agents is not generally employed because the effect is fleeting.

TRAVIS WINSOR, M.D., F.C.C.P.[*]
Los Angeles, California

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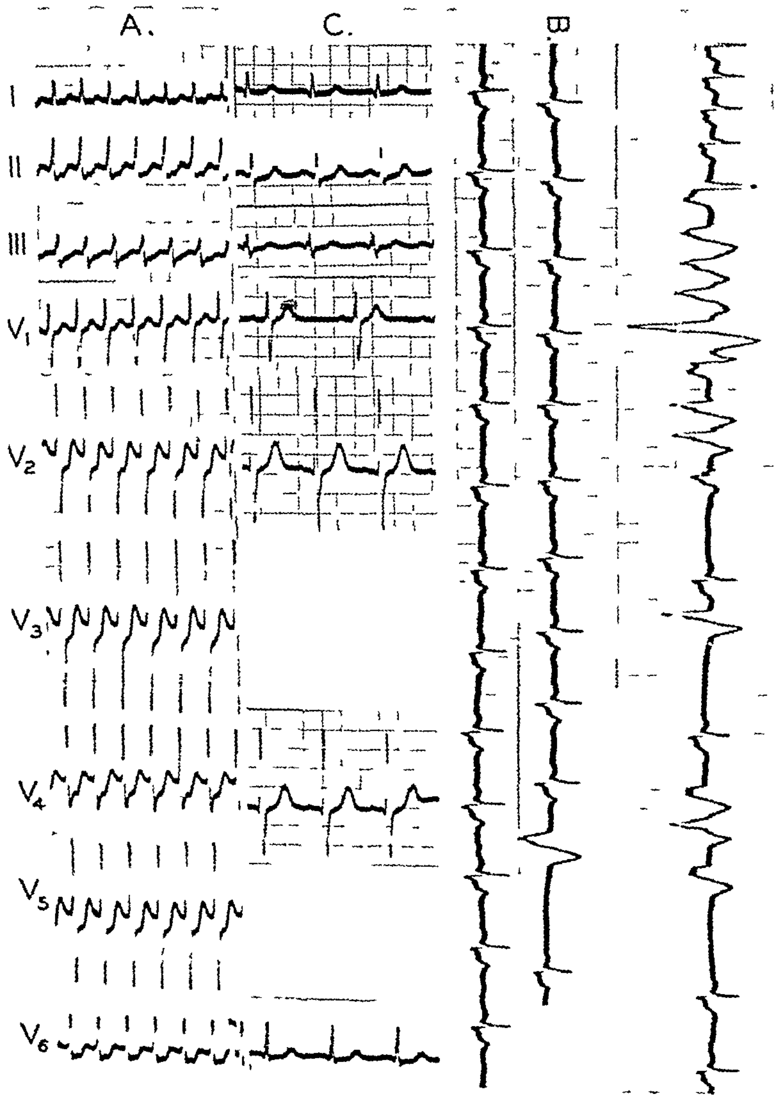
[*] From the Heart Research Foundation; The Nash Cardiovascular Research Foundation, The Hospital of the Good Samaritan, and the University of Southern California Medical School, Department of Medicine, Los Angeles.

THE ELECTROCARDIOGRAM OF THE MONTH

The authors would be pleased to receive comment and controversy from readers in relation to explanations offered.

A 53 year old woman has had attacks of paroxysmal supraventricular tachycardia about three to four times a year for the past 15 years. She has been known to be hypertensive (220/110) for the same period of time. During the past eight years the tachycardia is soon accompanied by pain in the chest and in the left arm. Recently she appeared in the office with one of these attacks and electrocardiogram *A* was recorded. While lead II was being recorded continuously *(B)* carotid sinus stimulation was applied. Five minutes later record *C* was obtained.

Interpretation: The RS-T shifts observed during the tachycardia *(A)* can hardly be attributed entirely to the very rapid rate. Since they were so pro-



nounced and were accompanied by pain in the chest and the left arm it was decided that they should be followed. Following return to sinus mechanism with very much reduced ventricular rate it is noted that the RS-T shift in part persisted for some time (*B*). After five minutes (*C*) only a very slight shift remains. It was felt that the persistence of the shift demonstrated here implied that a degree of subendocardial "injury" similar to that which occurs in many anginal attacks resulted from the excessive rate. Of course it should be remembered that occasionally an attack of angina will be responsible for supraventricular tachycardia.

Incidentally, when the carotid sinus stimulation induced arrest a short period of ventricular tachycardia occurred *(B)*. This alone is of some interest.

MANUEL GARDBERG, M.D., and IRVING L. ROSEN, M.D.*
New Orleans, Louisiana

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*Cardiac Research Laboratory, Touro Infirmary and the Department of Medicine, Louisiana State University Medical School.

Case Report Section

Congenital Aortic Stenosis, Coarctation of the Aorta and Patent Ductus Arteriosus: Report of Two Cases*

ELIAS G. PAPPAS, M.D.,** DIMITRI P. LAZARIDES, M.D.***
and DANIEL F. DOWNING, M.D., F.C.C.P.†
Philadelphia, Pennsylvania

Aortic stenosis combined with coarctation of the aorta has been reported by a small number of writers. In 1955 Smith and Matthews[1] were able to collect 24 autopsied cases from the literature. Marquis and Logan[2] have listed three additional patients. The clinical diagnosis has been made in a few others.[1, 3, 4] In the majority of instances the aortic stenosis was believed to be an acquired lesion.[1] That the combination is more common than these figures would indicate and that the aortic stenosis may frequently be of congenital origin is attested by its presence in eight of 37 individuals reported by one of us[5] in whom the stenosis could not be considered to be acquired.

Two patients have been seen who, in addition to congenital aortic stenosis and coarctation of the aorta, had a patent ductus arteriosus. Because the ductus introduces certain further physiologic and therapeutic problems, these cases are being reported.

Case Reports

Case 1: E. M., boy age 14. A diagnosis of congenital heart disease had been made at age three months. When he entered elementary school it was noted that on moderate exertion he would tire and become short of breath more quickly than his contemporaries. His activities had always been restricted by the parents. Occasional headaches and frequent epistaxis had been present. There had been no illness suggestive of the rheumatic state.

On physical examination, he was found to be well developed and nourished. There was no cyanosis. Carotid pulsations were visible at rest and the jugular veins were slightly distended. There was a prominent venous pattern over the anterior thorax. The heart was enlarged to the left and downward. A strong systolic thrill was palpable in the second and third right interspaces and over the neck vessels. A feeble systolic thrill was felt posteriorly to the right of the second and third thoracic vertebrae. The cardiac rate was 92/minute and there was a normal sinus rhythm. The sounds were normal. A loud harsh systolic murmur was best heard in the second and third interspaces to the right of the sternum and was transmitted over the entire thorax and to the neck. The right radial pulse was stronger than the left. No pulsation was felt over the arteries of the legs. Blood pressure in the right arm was 112/98; in the left, 102/90. No reading could be obtained in the lower extremities.

On the basis of these findings, diagnoses of aortic stenosis and coarctation of the aorta were made. He was admitted for study.

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*From the Division of Pediatrics, Hahnemann Medical College, and The Bailey Thoracic Clinic.

**Senior Fellow in Cardiology, Hahnemann Medical College and Hospital.

***Senior Fellow in Thoracic Surgery, Hahnemann Medical College and Hospital.

†Associate Professor of Pediatrics, Hahnemann Medical College and Hospital.

Laboratory Data—The electrocardiogram showed left bundle branch block and left ventricular hypertrophy.

On films and fluoroscopy the pulmonary vascular markings were normal. The main pulmonary artery and its right and left branches were normal. In the postero-anterior view the ascending aorta could not be defined. The heart was enlarged 2 plus in mass with rounding of the left border. In the left anterior oblique view the ascending aorta was dilated 2 plus. The data obtained by right heart catheterization are presented in the Table.

Hospital Course—From the catheterization there was evidence of a left to right shunt at the level of the great vessels. This was believed to indicate the presence of a patent ductus arteriosus. The pressure in the right ventricle, pulmonary artery and pulmonary venous capillary bed was elevated. The brachial artery tracing was abnormal, there being a delay to the peak of systole and a notch on the anacrotic limb near the summit. The dicrotic incisura was distinct.

Thoracic aortography was performed to delineate the coarctation believed to be present. The catheter could not be guided into the ascending aorta. Fifteen cc.'s of 70 per cent diodrast were injected in the region of the origin of the left subclavian artery. A short area of coarctation was demonstrated.

He was operated upon by Dr. Charles P. Bailey. When the isthmus of the aorta was dissected free, it was found that the patent ductus measured 0.5 cm. in diameter. It joined the aorta in the area of coarctation. There was a diffuse systolic thrill over the pulmonary artery and ascending aorta. The ductus was divided in the usual fashion. The coarcted segment of the aorta was then resected and an end-to-end anastomosis performed. The thrill over the pulmonary artery could no longer be felt. Through an incision in the myocardium of the left ventricle the aortic dilator was then introduced and the head guided to the region of the valve. The expanding arms were cautiously opened and the stenosed valve dilated. The thrill over the ascending aorta was now definitley less prominent.

Postoperatively the systolic murmur in the second and third interspaces was decreased in intensity and the thrill less marked. There was present a faint early diastolic murmur in the same area. No other sign of aortic insufficiency was found.

Case 2: M. B., girl age 6. A diagnosis of aortic stenosis was made at the age of two years. Her exercise tolerance had always been limited and she would become short of breath on moderate exertion. Profuse perspiration had been noted. Headache was a frequent complaint and she occasionally became dizzy after exertion. Left chest pain had been present on two occasions. The circumstances were not recalled. During the two months prior to admission she frequently said that her legs had "gone to sleep."

On physical examination she was well developed and nourished. The bony thorax was asymmetrical, the left anterior thorax being more prominent than the right. The heart was perhaps slightly enlarged to the left on percussion. There was a systolic thrill in the second and third right interspaces which could be felt over the neck vessels. The cardiac rate was 84/minute and there was a normal sinus rhythm. The second sound at the base to the right of the sternum was faint. A loud harsh systolic murmur was best heard in the second and third right interspaces and was transmitted over the anterior chest and to the neck. A systolic murmur of different character, softer and blowing, was heard over the posterior thorax. Femoral pulsations were weak. Blood pressure was 122/60 in the right arm, 106/80 in the left arm. It could not be determined in the legs.

Laboratory Data—The electrocardiogram showed left ventricular hypertrophy. On films and fluoroscopy the pulmonary vascular markings were accentuated 2 plus. The

TABLE I
CATHETERIZATION DATA

	O_2 Content (Vol. %) (Average of Three Samples)				Arterial Saturation	Pressure (Mm. Hg.)				
	VI	RA	RV	PA		RA	RV	PA	PVC	BA
E. M.	13.2	12.7	12.0	13.1	93 %	(0)	40/0	42/25	(20)	90/60
M. B.	10.4	9.9	9.6	11.0	91 %	(0)	70/0	70/55	(15)	80/60

Key: VI—venous inflow. RA—right atrium. RV—right ventricle.
PA—pulmonary artery. PVC—pulmonary venous capillary.
BA—brachial artery.
Figures in parentheses indicate mean pressure.

main pulmonary artery was dilated 2 plus as was its right branch. The left branch could not be defined. The ascending aorta was dilated and the knob prominent. The heart was enlarged 2 plus to the left with lengthening of the left border. In the left anterior oblique view there was 2 plus posterior prominence of the cardiac shadow. The data obtained by right heart catheterization are presented in the Table.

Hospital Course—From the catheterization there was evidence of a left to right shunt at the level of the great vessels. The pressure in the right ventricle, pulmonary artery and pulmonary venous capillary bed was elevated. The brachial artery tracing showed a slow rise to the peak of systole.

Thoracic aortography was performed to define the extent of aortic coarctation. It was found to be confined to a short segment just distal to the left subclavian artery. There was a suggestion of simultaneous opacification of aorta and pulmonary artery.

The child was operated upon by Dr. Charles P. Bailey. Over the ascending aorta and pulmonary artery a systolic thrill was felt. The ductus was found to be 1 cm. by 1 cm. and to join the aorta in the area of coarctation. It was divided and the narrowed area of the aorta resected. Aortic valve dilatation was then carried out via the tran-ventricular route. No thrill could now be felt over the pulmonary artery and that over the ascending aorta was softer and more diffuse.

The postoperative course was uneventful. The murmur and thrill in the second and third right interspaces were now much less prominent. The posterior systolic murmur could no longer be heard.

Discussion

This complex of anomalies is unusual in that for each malformation a satisfactory surgical procedure exists. The recognition of the presence of all of the components and of their relative severity is necessary.

The murmur and thrill of aortic stenosis were unmistakable in both of these patients. Nothing was heard which would suggest a patent ductus arteriosus. Knowledge of its existence required catheterization. The character of the peripheral pulses was of importance in the diagnosis of coarctation. Femoral pulsations were weak. Although the blood pressure in the arms was not elevated, that in the legs could not be measured. The aortic stenosis, interfering with left ventricular output at a proximal level, discouraged the development of the hypertension in the aortic arch and its vessels which would be present in uncomplicated coarctation.

Assessment of the relative importance of the defects properatively depended upon consideration of the electrocardiogram and the catheterization data. In both patients, there was a pattern of left ventricular hypertrophy. Each of the lesions may cause this. It was obvious that the coarctation did not contribute in these patients because of the lack of hypertension in the arch. In other words, under the circumstances, the coarctation demanded no extra work on the part of the left ventricle. The specific effect of the ductus could not be determined. Flow could have been greater in the past and might have required ventricular hypertrophy. Pulmonary vascular changes taking place over a period of time would then have decreased the shunt. However, the observations in regard to the relative importance of the stenosis and the coarctation indicated that the stenosis must be more important than the ductus.

It followed that relief of the aortic stenosis must be the prime consideration in therapy. If the coarctation were to be resected and the ductus interrupted without relieving the stenosis, the burden on the left ventricle would remain. It was clear, too, that were the stenosis alone attacked there would still be a major and a minor cause of left ventricuar over-work. It was obvious that all three defects must be corrected during the same operation.

REFERENCES

1 Smith, D. E. and Matthews, M. D.: "Aortic Valvular Stenosis with Coarctation of the Aorta. With Special Reference to the Development of the Aortic Stenosis upon Congenital Bicuspid Valves," *Brit. Heart J.*, 17:198, 1955.

2 Marquis, R. M. and Logan, A.: "Congenital Aortic Stenosis and its Surgical Treatment," *Brit. Heart J.*, 17:373, 1955.

3 Grishman, A., Steinberg, M. F. and Sussman, M. L.: "Congenital Aortic and Subaortic Stenosis with Associated Anomalies of the Aorta," *Med. Clin. North Am.*, 31:543, 1947.

4 Gilbert, R. L., Riordan, J. J. and Murphy, J. P.: "Coarctation of the Aorta of Adult Type Associated with Acquired Aortic Stenosis," *Missouri Med. Assoc. Jour.*, 47: 333, 1950.

5 Downing, D. F.: "Congenital Aortic Stenosis. Clinical Aspects and Surgical Treatment," *Circulation*, 17:373, 1955.

Atrioventricular Nodal Rhythm with Antegrade Block

HIROYOSI MORI, M.D.* and B. J. ALLENSTEIN, M.D., F.C.C.P.

Duarte, California

Atrioventricular nodal rhythm is an infrequent, electrocardiographic finding in which the pace-maker has shifted from the sinus node to the atrioventricular node. The characteristic electrocardiographic findings of this rhythm are as follows:[1-6]

1. In the limb leads the P waves are inverted in II, III, and aVF, and are upright in aVR, aVL and I (small amplitude).
2. It is usually associated with bradycardia.
3. The PR interval may vary from 0.12 second to negative value, i.e., an RP interval.

Nodal rhythms are classified as upper, middle, and lower nodal rhythm according to the positions of the retrograde P wave to the QRS wave. This classification is based on the assumption that the impulse originates from a nodal focus and spreads at normal speed in upper and lower directions. If there is some conduction disturbance of the nodal impulse on its way to the auricle (retrograde block) or ventricle (antegrade block), this classification can not be used.[1] A PR interval of more than 0.12 second can be observed in cases of atrioventricular nodal rhythm associated with antegrade block.[1, 3, 6] Because of its rarity, we are reporting an atrioventricular nodal rhythm with antegrade block observed during cardiac surgery and later spontaneously in the post-operative period, in which the auricular conduction was delayed as long as 0.25 second.

Case Report: J. B., a 56 year old white man, was admitted to the City of Hope Medical Center on October 22, 1956. He had developed shortness of breath on exertion one and one-half years before admission. He also had nocturnal dyspnea, orthopnea, and palpitation which had been treated with digitalis and mercurials with improvement. For several months prior to admission his symptoms worsened. He had no past illness except for Tetanus five years previously.

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*Fellow, from Tokushima University, Japan.

From the Hospital for Cardiac Disease and The Medical Research Institute, City of Hope Medical Center.

The blood pressure was 102/90. There were no rales in the chest. The point of maximum impulse was in the left fifth intercostal space at the mid-clavicular line. There was a Grade IV systolic murmur and a palpable thrill at the aortic area which was transmitted into the neck. There was a Grade I to II aortic, diastolic murmur best heard in the left third intercostal space at the sternal border. The liver, kidney, and spleen were not palpable, and there was no peripheral edema.

Laboratory Findings: The laboratory findings including urine, routine blood chemistries, and serological tests for syphilis were within normal limits.

X-ray examination revealed the heart enlarged in its transverse diameter with rounding of the left heart border due to left ventricular hypertrophy. The aorta was elongated with some dilatation distal to the aortic valve. Dense calcification was seen in the region of the valve. The left auricle was also enlarged, displacing the esophagus posteriorly.

A direct blood pressure recording from the brachial artery measured 80/54 mm. of Hg., with a typical aortic stenosis pressure curve. The diagnosis of aortic stenosis with slight degree of aortic insufficiency was made.

An aortic commissurotomy was performed on November 9, 1956. At surgery, marked post-stenotic dilatation of the aorta was found, and a marked systolic thrill was felt in this area. He tolerated the commissurotomy well. However, several days post-operatively, congestive cardiac failure ensued. He failed to respond to increased digitalization, mercurials, etc., and died on the eighth post-operative day, November 16, 1956.

The post-mortem revealed a markedly hypertrophied and dilated right and left ventricle, with a markedly calcified stenotic aortic valve. There was no evidence of myocardial infarction in either ventricle, septum, or in the auricles.

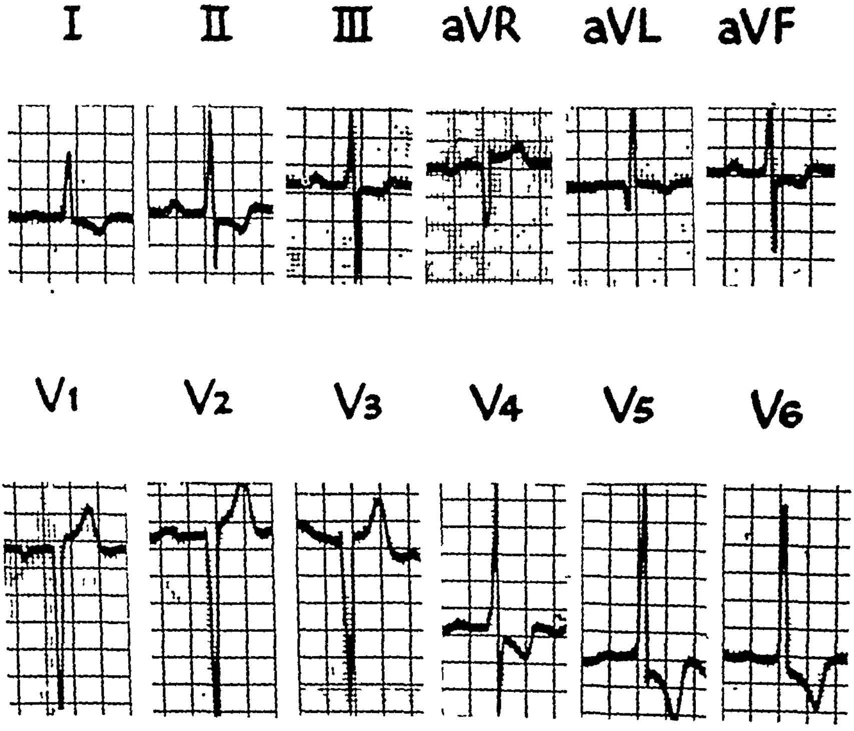

FIGURE 1: Pre-operative electrocardiogram. Note the PR interval 0.26 seconds, and the P wave; upright in Leads I, II, III, aVF, and inverted in aVR and aVL. The ventricular heart rate was 76 per minute.

The first electrocardiographic tracing (Figure 1) taken October 22, 1956, was interpreted as an abnormal electrocardiogram, with left ventricular hypertrophy, first degree atrioventricular block, and digitalis effect and/or myocardial injury and ischemia. The P wave was upright in all the standard limb leads and V_1 through V_6; was inverted in aVR, and diphasic in aVF. The PR interval was 0.26 seconds. The heart rate was regular at 76 per minute.

The electrocardiogram taken on the morning of the operation (November 9, 1956) was essentially the same except for a sinus tachycardia of 107 per minute. Immediately after the chest was entered, auricular fibrillation with a ventricular rate of 150 per minute occurred. In a few minutes normal sinus rhythm was re-established spontaneously with a PR interval of 0.28 seconds (Figure 2A). This change from sinus rhythm to auricular fibrillation to sinus rhythm subsequently occurred six times. After these changes the following interesting alteration occurred. Sharply inverted P waves were observed in Lead II with a PR interval of 0.25 seconds (Figure 2B). After a few minutes, sinus rhythm occurred spontaneously (Figure 2C). These changes recurred three times during the surgery.

The electrocardiogram upon completion of the surgery was the same as preoperatively.

On the second post-operative day, the deeply inverted P wave was again noted in

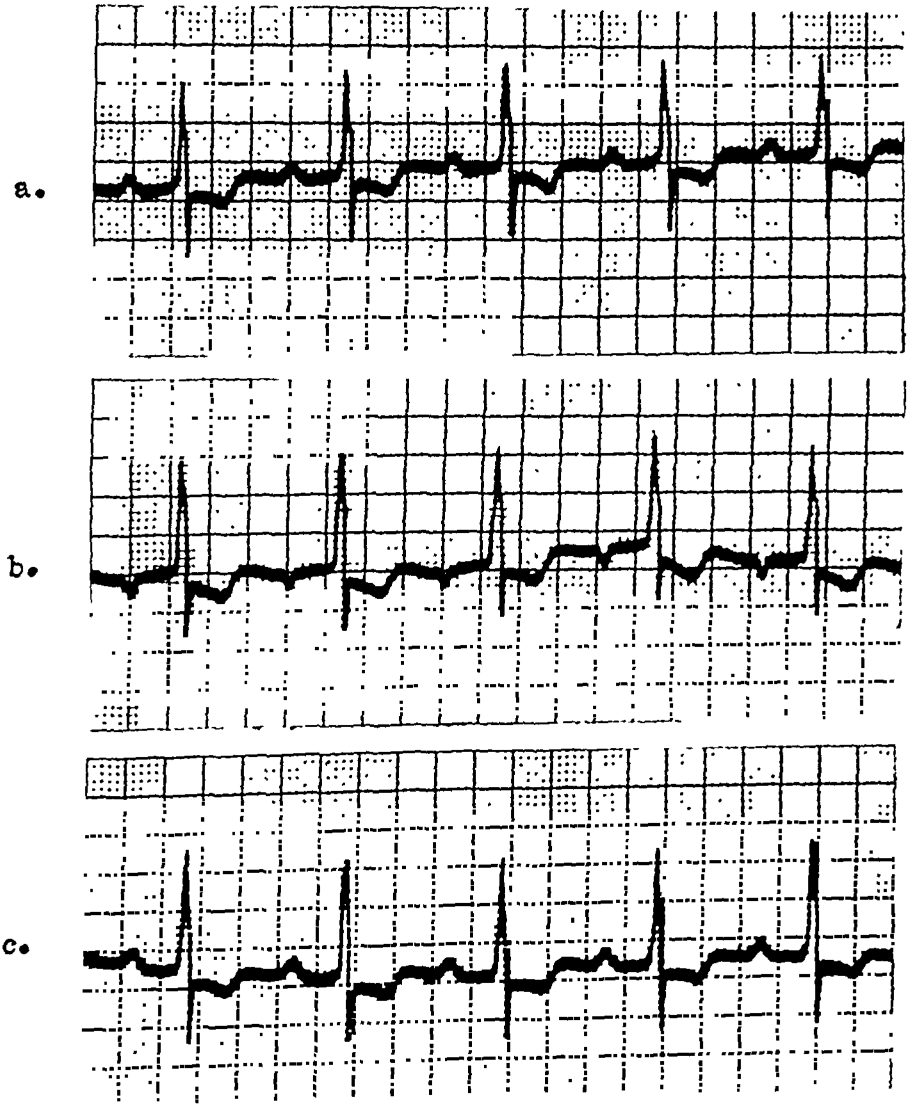

FIGURE 2: Lead II only. (a) at start of surgery, (b) antegrade block, atrioventricular rhythm during surgery, PR interval is 0.25 seconds and (c) spontaneous return to normal sinus rhythm.

Leads II, III, and aVF with an upright P wave in Lead I aVR and aVL (Figure 3). The chest leads were not taken because of the operative wound. The PR interval in Lead II was 0.22 seconds.

On the following day auricular fibrillation recurred and persisted.

DISCUSSION

The outstanding features of this case are the sharply inverted P waves in Lead II, III, aVF and marked prolongation of the PR interval. Before the shift of the pace-maker from the sinus to the atrioventricular node, this patient had evidence of disturbance of auricular conduction as demonstrated by a first degree A-V block with a normal sinus rhythm.

Langendorf and co-worker[1] concluded that the classification of atrioventricular nodal rhythm as upper, middle, and lower nodal rhythm is not suitable in the presence of atrioventricular block. Retrograde (depression of the impulse conduction to the auricle) will shorten the PR in-

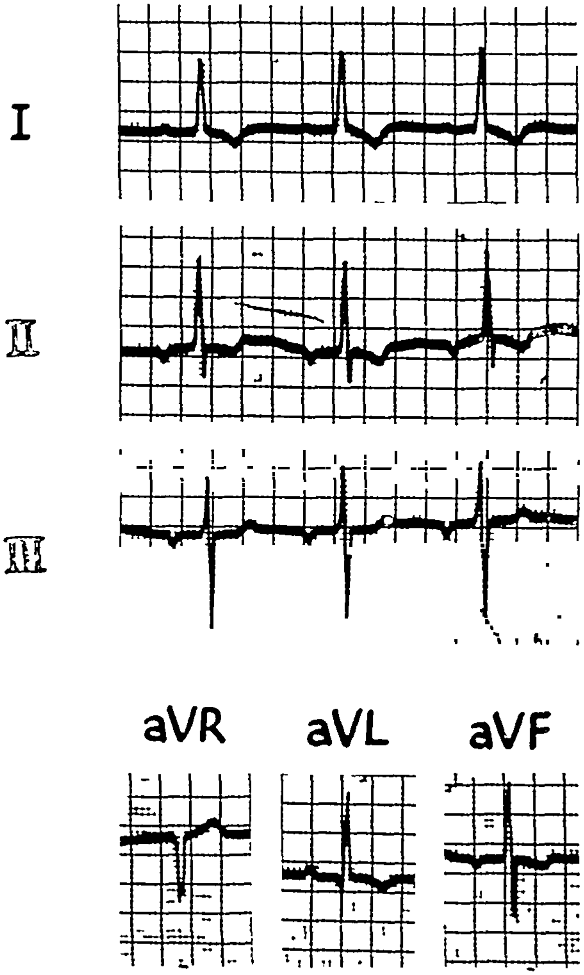

FIGURE 3. Limb leads taken on second post-operative day. The rate is 72 per minute. P is upright in I, aVR, aVL, inverted in II, III, aVF. PR interval is 0.22 seconds.

terval and tend to convert it into an RP interval. Antegrade block (depression of the impulse conduction to the ventricle) will prolong PR interval and tend to convert an RP into a PR interval. They reported one case with antegrade block, the PR interval measuring 0.18 sec.

Vakil[3] reported two cases of atrioventricular nodal rhythm with antegrade block. One of them, an elderly, hypertensive patient with acute pulmonary edema, had a PR interval of 0.16 second. The other patient showed three different types of rhythm besides normal sinus rhythm, namely (a) uncomplicated upper nodal rhythm, (b) nodal tachycardia with two to one atrioventricular antegrade block, and (c) nodal tachycardia with instances of two to one block, first degree heart block and nodal pause. The PR interval of the case was 0.09-0.10 sec. One complex showed a PR interval of 0.20 sec. followed by retrograde P wave.

Bix[6] reported three interesting cases of nodal rhythm with A-V block. One of them showed A-V nodal rhythm with A-V block in form of Wenckebach phenomenon.

The electrocardiogram of our patient showed A-V nodal rhythm with antegrade block, in which PR interval measured 0.25 seconds. This is a larger PR interval associated with atrioventricular nodal rhythm with antegrade block than we could find in any other paper.

REFERENCES

1 Langendorf, R., Simon, A. J. and Katz, L. N.: "A-V Block in A-V Nodal Rhythm," *Am. Heart J.*, 27:209, 1944.

2 Goldberger, E.: *Unipolar Lead Electrocardiography*, Lea & Febiger, Philadelphia, 1949.

3 Vakil, R. J.: "Auriculoventricular Nodal Rhythm with Heart Block," *Am. Heart J.*, 46:845, 1953.

4 Scherf, D.: "Ueber den atrioventricularen Rhythmus," *Zsch. f. d. ges. exp. Med.*, 78:511, 1931.

5 Barker, J. M.: *The Unipolar Electrocardiogram*, Appleton, New York, 1952.

6 Bix, H. H.: "A-V Nodal Rhythm with Various Types of A-V Block," *Sinai Hospital J.*, 2:42, 1953.

An Unusual Cause of Massive Hemothorax

SYDNEY BASSIN, M.D., F.C.C.P.* and FARHAN BAKIR, M.B., Ch.B.**
New York, New York

Although intestinal obstruction and strangulation as a complication of traumatic diaphragmatic hernia are well recognized and have been reported frequently since the first case was described by Pare in 1564,[1] massive bloody pleural effusion has been seldom associated with strangulation. The paucity of the symptoms referred to the abdomen in this case is most unusual.

O. M., a 33 year old colored man, was admitted on December 9, 1954, complaining of shortness of breath and swollen abdomen.

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*Director of Pulmonary Disease, City Hospital.

**Chief Resident in Medicine, City Hospital. (Fulbright Scholar from Iraq)

He had led an apparently uneventful existence with no serious illness until one week prior to admission when he developed a "cold" followed by cough productive of about an ounce of mucoid sputum daily. Five days prior to admission he experienced a sharp pain over the lower and lateral part of the left chest, which was aggravated by cough and deep inspiration. This condition progressively deteriorated and he developed increasing shortness of breath. He became aware of abdominal swelling in the last two days. The last bowel movement occurred two days prior to admission to the hospital. He experienced no abdominal pain or vomiting. Interrogation revealed that abdominal distension had occurred on many occasions in the past and had been relieved by infrequent bowel movements.

He was a moderate smoker but had over-indulged in alcoholic beverages for the past 10 years.

Physical examination revealed an acutely and extremely ill individual in severe respiratory distress, sweating profusely. The facial expression was anxious and apprehensive. The pulse rate was 120 per minute, regular but of low volume. Rectal temperature was 101.2° F., and respiration attained a rate of 40 per minute and was shallow in character.

Examination of the eyes, ears, nose and throat revealed an essentially normal status except for slight hyperemia of pharyngeal mucosa. There was marked deviation of the trachea toward the right. There was no evidence of clubbing of the finger tips and no lymphadenopathy was palpable anywhere in the body. There were old healed scars on the face, left arm and in the left eighth intercostal space at the scapular line. The expansion of the left hemithorax was markedly limited.

Palpation revealed diminished tactile fremitus over the entire left hemithorax. Percussion elicited flatness over the same side except at the extreme apex. The apex beat was palpable in the right fourth intercostal space two inches to the right of the sternal border. Percussion of the cardiac dullness confirmed the palpatory finding. On auscultation the heart sounds were regular, rapid and best heard over the right hemithorax. The expiratory phase of respiration was prolonged and there were diffuse expiratory wheezes over the right lung. The breath sounds were faint and distant over the left hemithorax except at the apex.

The abdomen was moderately and uniformly distended but no tenderness or rebound tenderness could be elicited. Peristalsis was hypoactive.

Rectal examination and the remainder of the physical examination were unremarkable.

Laboratory findings were red blood cells 4,600,000 per cubic millimeter, hemoglobin 11 grams per cent, hematocrit 33 per cent, white blood cells 21,800 per cubic millimeter with shift to the left. Urine was normal. Serum analysis of the blood was 6 Winslow's units.

An x-ray film of the chest revealed a homogeneous density involving the entire left hemithorax. There was marked mediastinal shift toward the right. The dome of the left diaphragm could not be visualized. The findings were consistent with massive pleural effusion (Figure 1).

Thirty-three hundred cubic centimeters of grossly bloody fluid was aspirated from the left pleural space. The fluid had the appearance of thin dark venous blood. The hematocrit on this fluid was 5 per cent and it contained 460,000 red blood cells per cubic millimeter. The serum analysis value of the aspirated material was 4 Winslow's units. During thoracentesis, 1,000 cc. of blood were transfused to the patient, which raised the hematocrit from 33 to 39 per cent.

He improved subjectively and objectively following thoracentesis and transfusion. A subsequent x-ray film demonstrated that the upper limit of the homogeneous density in the left hemithorax had descended to the level of the fourth costal cartilage anteriorly. A large circumscribed area of radiolucency in the left apex, which was interpreted as localized pneumothorax, was visualized. The mediastinum returned to a median position; the dome of the left diaphragm was still not demonstrable (Figure 2). X-ray examination of the abdomen showed a small and large bowel distension with fluid levels (Figure 3).

Abdominal decompression was attempted by continuous Wangensteen suction. Nothing was given by mouth but intravenous fluids were administered together with wide range antimicrobial drugs.

Surgical consultation resulted in the opinion that the abdominal distension was due to paralytic ileus. Normal saline, soap and water and warm olive oil enemas were unsuccessful and the abdominal distension was unaffected by attempts at oral and rectal decompression.

He developed a coarse tremor of the hands and lips and was incoherent and irrational. By the second hospital day he was in frank "delirium tremens."

X-ray film of the chest on the third hospital day revealed diminution of the density

FIGURE 1

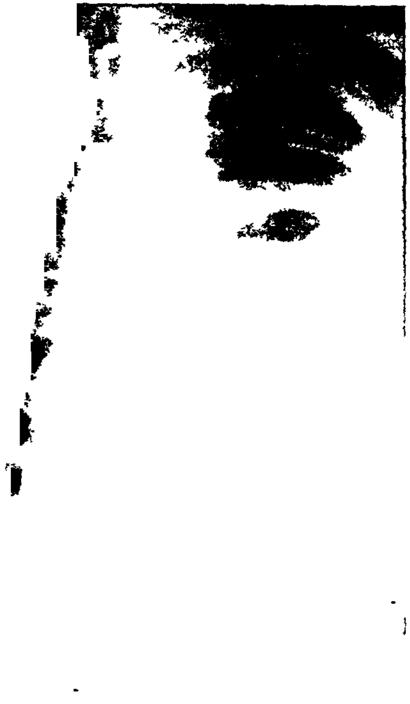

FIGURE 2

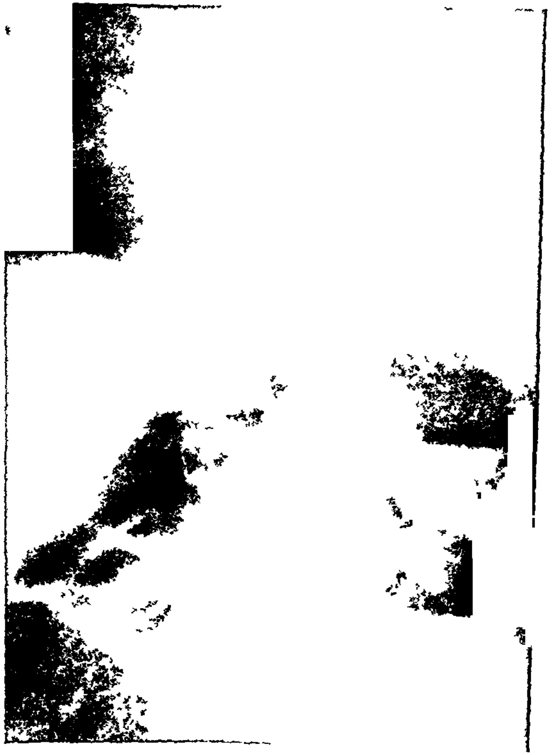

FIGURE 3

in the left chest. The left diaphragm was still not visualized but two fluid levels were seen in this area (Figure 4).

Seventy-two hours after admission, for the first and last time he vomited coffee ground material and expired 15 minutes later. The fluid aspirated from the chest was reported after death to be positive for anaerobic streptococci and E. coli on culture.

Autopsy showed abdominal distension. Old healed scars were present on the face, left arm and a third one, two inches in length, along the left eighth intercostal space in the scapular line. The gastrointestinal tract was markedly distended and covered with sero-fibrinous exudate. The descending colon was empty and collapsed below the splenic flexure.

The lungs revealed emphysematous changes in the upper lobes with emphysematous bullae in the apex of the left lung. The remainder of the left lung was atelectatic and covered by sero-fibrinous exudate and was firmly attached to the chest wall antero-laterally.

A loop composed of splenic flexure and part of the transverse colon was found in the left hemithorax. The loop was found to be edematous, hemorrhagic and necrotic. There was no peritoneal sac to this loop. The diaphragmatic opening was in the postero-lateral position of the left diaphragm. It was small with an organized plastic fibrous ring.

Microscopical examination of the strangulated loop showed destroyed mucosa with polymorphonuclear cell infiltration and fibrin deposition.

Discussion

Intestinal obstruction and strangulation are not infrequent complications of diaphragmatic hernia and are the most dangerous ones indeed. About 90 per cent of all cases of strangulated diaphragmatic hernia are traumatic.[2] Almost all the cases reported, or 98.4 per cent are left sided[1] for obvious anatomical reasons.

Pleural effusion accompanying strangulation of herniation through the diaphragm is not an unusual finding and has been detected clinically, radiologically, through thoracotomy, or at autopsy, on many occasions. The character of the fluid may be serous[4] but is often serosanguinous because of the underlying physio-pathology.

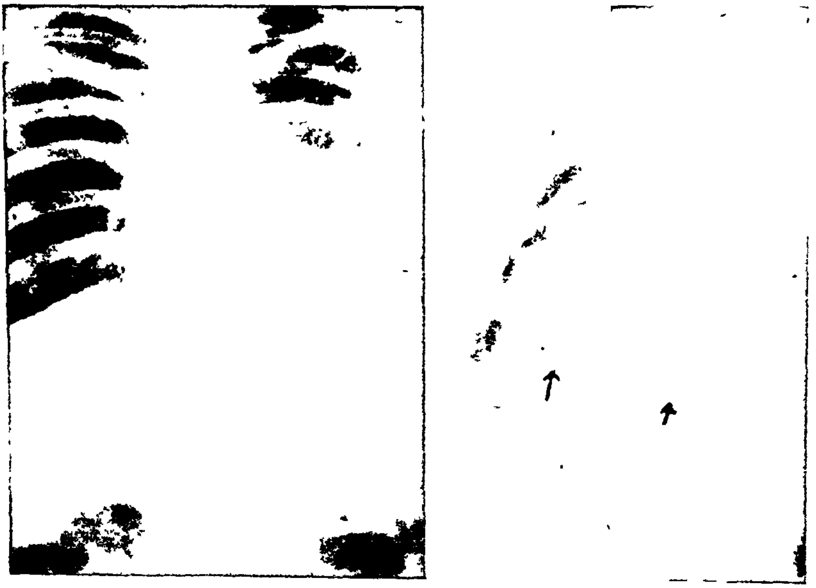

FIGURE 4

Although bloody pleural effusion was described as early as 1858 as a fortuitous finding by Alderson during an autopsy of a case of strangulated diaphragmatic hernia with perforation of the stomach,[5] massive hemothorax has been rarely encountered or reported.

We were able to find only three cases in the literature more or less comparable to the case being reported in respect to the amount and character of the pleural effusion.[2,6,7]

Deaner et al[8] described a case of hemothorax with strangulated diaphragmatic hernia with opacification of the left chest on x-ray film but the amount of fluid aspirated was only 37 cc. on two occasions. On autopsy the left hemithorax contained omentum and clotted blood.

However, this case is unique and different from all the cases previously reported in the paucity of abdominal symptoms and signs except for the distension which, together with the sluggish peristalsis and the absence of pain and vomiting, had been attributed to paralytic ileus.

In all the cases reported, the abdominal symptoms of pain, discomfort and vomiting were the predominant part of the clinical picture. Although chest pain, dyspnea and evidence of pleural effusion are common with strangulated diaphragmatic hernia, they have apparently never been so overwhelmingly the outstanding part of the clinical picture as to effectively mask the abdominal component.

The history of a "cold" as the onset of the present illness, the diffuse wheezing and evidence of bronchospasm, the presence of radiolucency which was interpreted as localized pneumothorax or a bulla, the massive bloody pleural effusion, the absence of abdominal pain, vomiting or tenderness, the sluggish peristalsis, in addition to complicating delirium tremens, directed attention to the respiratory system as the site of primary pathology.

Barium enema to investigate the cause of abdominal distension probably would have given the answer and would have resulted in the correct surgical approach to the problem. The patient expired before the clue given by the report of the culture of the pleural effusion was received and before further studies could be initiated.

REFERENCES

1 Pare, Lib. 9, Cap. cited by Reid, J.: "Case of Diaphragmatic Hernia Produced by Penetrating Wound," *Edenbor. M. and S. J.*, 53:104, 1840.

2 Carter, B. N. and Giuseppi, J.: "Strangulated Diaphragmatic Hernia," *Surgery*, 128:210, 1948.

3 Harrington, S. W.: "Various Types of Diaphragmatic Hernia Treated Surgically. Report of 430 Cases," *Surg., Gynec. and Obst.*, 86:735, 1948.

4 Brisbane, J.: "Intestinal Obstruction Secondary to Diaphragmatic Hernia," *J. of Mt. Sinai Hospital*, 18:362, 1952.

5 Alderson: *Lancet*, 2:396, 1858.

6 Pfahl, C. J. and Lund, H. Z.: "Strangulated Diaphragmatic Hernia and Sero-Sanguinous Pleural Effusion," *Ohio State M. J.*, 40:1158, 1944.

7 Pearson, S.: "Strangulated Diaphragmatic Hernia, Report of Four Cases," *A.M.A. Arch. of Surgery*, 66:155, 1953.

8 Deaner, S., McMenemey, W. H. and Smith, S. M.: "Hemothorax Due to Strangulated Diaphragmatic Hernia," *Brit. M. J.*, 1:72, 1943.

Artificial Pneumothorax in the Treatment of Pulmonary Tuberculosis
With Case Reports

HANS KUMAR, M.B., B.S., F.C.C.P.*
Jaipur, India

Pneumothorax was the first effective form of collapse therapy to be used widely. During the first 40 years of the present century, it attained world-wide acceptance, becoming at one time the standard and almost universally preferred method of pulmonary collapse. During recent years, its popularity has diminished to a marked degree especially in the United States; some large Tuberculosis Institutions having abandoned it completely. In this hospital, we do not use pneumothorax as a routine therapeutic procedure, our patients are treated on pneumoperitoneum and chemotherapy followed by major chest surgery. However we do feel that in some circumstances, no other measure is likely to be useful and the following case reports are presented with that object.

Case 1: This 22 year old man was admitted to the hospital with severe hemoptysis but gave no previous history of tuberculosis. An x-ray film on admission showed evidence of exudative infiltration with break down in the right upper zone (Figure 1). Absolute rest, sedation with morphia and coagulants were given along with chemotherapy but recurrent and profuse hemoptysis continued. His condition deteriorated and he became moribund: Artificial pneumothorax on the right side was induced and the hemoptysis stopped immediately. X-ray film showed collapse of right lung with apical adhesion. He has improved clinically and is advised to undergo pulmonary resection.

Case 2: This 30 year old man was admitted with far advanced bilateral pulmonary tuberculosis more extensive in the left upper and mid zone (Figure 2). He was treated on bed rest, pneumoperitoneum and chemotherapy. After nine months he did not show radiological improvement; recurrent hemoptysis started and his general condition gradually deteriorated. To stop hemoptysis, artificial pneumothorax was induced on the left side. This did not permit complete relaxation of the diseased area but produced sufficient alteration of intrapulmonary mechanics to stop bleeding. His general condition improved, there was no recurrence of bleeding, his disease on the contralateral side regressed and a seven rib thoracoplasty was done on the left side.

Though artificial pneumothorax is not often used in the treatment of hemoptysis, the above two cases remind us that it may be valuable and its use should not be relegated entirely to the realms of history.

Case 3: This case demonstrates indication of pneumothorax in cases where pneumoperitoneum and chemotherapy has failed to close cavities in patients in whom the lesion is not considered more suitable for resection or surgical collapse.

This 35 year old man was admitted with bilateral advanced pulmonary tuberculosis with multiple cavities in the left lung. Treatment with pneumoperitoneum, bed rest and chemotherapy for one year failed to bring radiological improvement, the cavities persisted and the disease with contralateral lung did not show regression (Figure 3). His general condition was poor and he was producing a large amount of sputum positive for acid fast bacilli. Pneumothorax was induced on the left side and the adhesions were cauterized by closed intrapleural pneumonolysis (Figure 4). His general condition has improved, sputum is negative for acid fast bacilli and the disease in the contralateral lung has regressed. He is now ready to undergo major chest surgery.

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*Medical Superintendent, Tuberculosis Sanatorium.

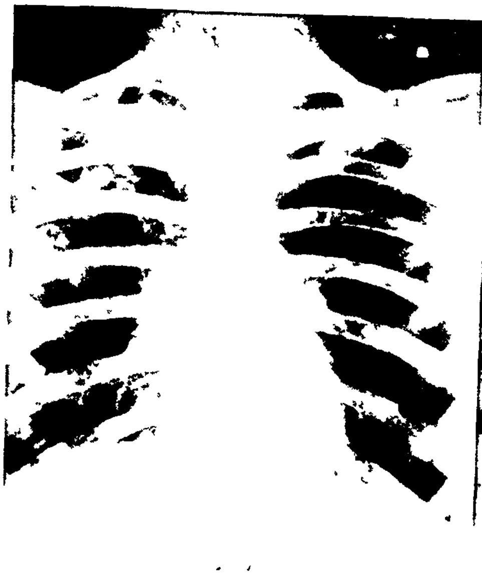

FIGURE 1

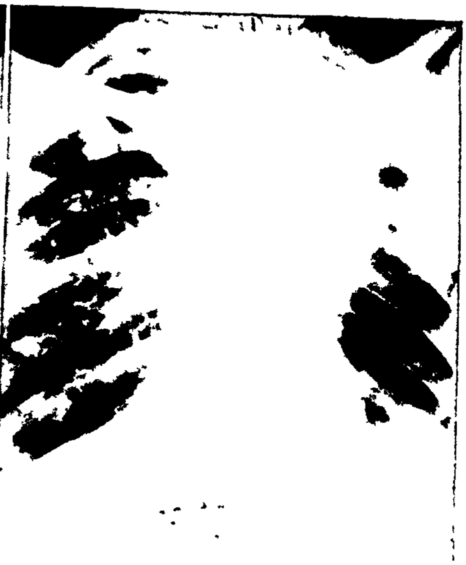

FIGURE 2

Figure 1: Exudative infiltration with breakdown right upper zone.—*Figure 2:* Left upper and mid zone extensive disease with cavities. Right mid zone disease with cavity.

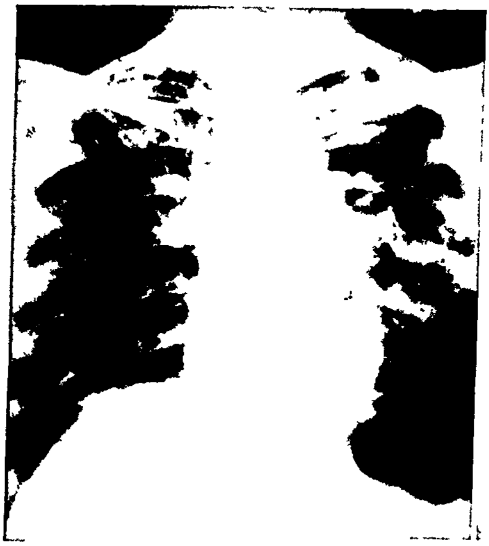

FIGURE 3

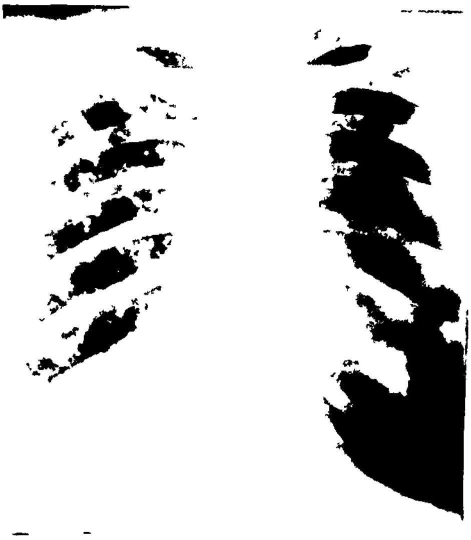

FIGURE 4

Figure 3: Left upper and mid zone cavity persists. No change in disease elsewhere.—*Figure 4:* Collapse left side—Upper lobe well collapsed.

BIBLIOGRAPHY

Carruthers, K. J. et al.: "Artificial Pneumothorax in Hemoptysis," *Brit. J. Tuberc.*, Jan., 1956.

Hickling, R. A.: "Hemoptysis," *British Encyclopedia*, 1951, 1955.

Lloyd, Rusby: "Hemoptysis," *Med. Illus.* (London), 1955.

The Meaning of International Congresses

As a participant in and as one of the organizers of the international congresses on diseases of the chest held in Rome, Italy, in 1950; Rio de Janeiro, Brazil, in 1952; Barcelona, Spain, in 1954; and in Cologne, Germany, in 1956; I have had ample opportunity to appraise critically their role and value in world affairs.

These congresses were organized under the sponsorship of the American College of Chest Physicians. The College, a symbol of lofty ideals in the healing arts, has been a leader in the international development of undergraduate and postgraduate medical education, and a standard bearer in the dispersement of scientific knowledge.

These congresses evolved from the desire for better international understanding and good will. It should not be surprising, therefore, that they have received universal approbation of the medical profession of the world. Thus, these congresses occupy a rightful, permanent place in medical events and are used as models by other groups. These congresses make possible the prompt and maximal dissemination of important scientific news.

The scientific program to be presented at the Fifth International Congress on Diseases of the Chest in Tokyo, September 7-11, will cover many surgical and clinical aspects in the treatment of chest diseases. Tuberculosis and carcinoma of the lung, other infections, diseases of allergic origin, thoracic trauma, occupational disorders, parasitic infestations, tropical ailments, hazards of radio-active fall-out, pediatric cardiology, cardiorespiratory problems of the postnatal period and in geriatrics, will be included. Special attention will be paid to emphysema, metabolic and other systemic affections involving the lungs and heart. Due time will be devoted to diseases of the esophagus, mediastinum and the diaphragm, as well as to recent advances in diagnostic methods, including cytology, the use of isotopes and to cardiology. Consideration will be given to modern procedures in the use of antibiotics, chemotherapy, aerosols and physical therapy, with emphasis on rehabilitation of the respiratory invalid and the cardiac cripple. Aviation medicine and its anticipated interplanetary problems is of immense interest and demands due thought. Of course, the tremendous strides in thoracic and cardiac surgery require ample time commensurate with their importance.

In accordance with plans, eminent clinicians and research workers will participate in the transactions of the congress in formal lectures, fireside conferences, and in panel discussions. You are likely to hear some animated, spirited debates on these occasions.

The program will be augmented by scientific motion pictures and scientific and technical exhibits which are highly instructive.

What is the explanation of the unprecedented success of the international congresses of the College? It is axiomatic that the value of human life to the individual is the same in the lowest as in the highest socio-economic strata of society; it is the same in small countries as in large ones; it is the same in the temperate zone as it is in the tropics or at the Arctic. Obviously, as long as disease remains the common enemy of mankind, as long as it spreads in global dimensions—as we have witnessed recently in the form of Asian influenza—it is unwise to confine medical science within regional or national boundaries. Scientific isolationism cannot be condoned. It is deplorable from the viewpoint of all ethical standards of medicine. Actually, its fallacious egotism hurts the isolationists themselves no less than it hurts the welfare of their patients.

The international congress offers a wonderful occasion for meeting doctors of all nationalities. Psychologically, contact with others is destined to dispel fear, reserve and the admittedly primitive but powerful instinct of "dislike of the unlike." No doubt, these international conventions are the best antidote for discrimination and prejudice.

If you attend with an open and receptive mind, you cannot fail to realize that the scientific discoveries presented by notable pioneers arouse a desire for an accelerated tempo of inquisitiveness toward hitherto unfathomed health problems. Veritably, a congress of this sort imparts catalytic influences in inspiration and awareness. Ideas gathered there are likely to sharpen one's focus on relevant entities, set into motion new trends of thoughts and may rectify vague notions and reveal flaws in our own seemingly accurate reasoning.

Of course, there is a lighter side to the congress too. The warm hospitality of our hosts and their proverbial generosity will leave a lasting impression. Needless to say, there will be the enchanting, picturesque scenic beauty of Japan. When, at the conclusion of the meetings, you bid adieu, you will leave the congress with worthwhile scientific knowledge and with cherished, warm sentiments for new friends.

ANDREW L. BANYAI, M.D., F.C.C.P.*
Milwaukee, Wisconsin

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*Chairman, Council on International Affairs.

The President's Page

For the past six months the College journal has been publishing a series of articles concerning the physicians' role in promoting world peace. Prominent physicians in various parts of the world have contributed to this splendid series of editorials. Our Editor, Dr. Jay Arthur Myers, who initiated the series, wrote the first editorial which appeared in the September 1957 issue. No doubt other members of the College have thoughts on this important subject and I am sure that the Editorial Board would be pleased to consider articles if they wish to submit them. World peace is of vital importance to everyone and the physician, who is concerned with life itself, must play an important part.

I should like to call your attention to the Section on Cardiovascular Disease, which started with the January issue of the journal. This section was introduced because of the diversified interests of our members and the large number of members who specialize in cardiology. The Editorial Board would like to have your comments on the series of articles dealing with "Current Therapy in Cardiovascular Disease" and the "EKG of the Month." Contributions to these special sections may be submitted for consideration by the Board.

Plans for the 24th Annual Meeting of the College to be held in San Francisco, June 18-22, are progressing satisfactorily. The program will be published in the April issue of *Diseases of the Chest* and I know that all of our members will want to be present for these exceptionally fine scientific sessions.

The councils and committees of the College will hold their annual meetings at the Fairmont Hotel, San Francisco, on Thursday, June 19, and it is expected that all members will be present. Our councils and committees will function effectively only if all members attend the meetings and contribute to their respective programs.

I must call your attention once again to the fact that the hotel situation in San Francisco is critical. Members who plan to attend the annual meeting and who have not made their hotel reservations are urged to do so at once. A reservation coupon appears on page xxxii of this issue of the journal.

The Committee on Nominations, composed of Dr. J. Winthrop Peabody, Washington, D. C., Chairman, Dr. Sumner S. Cohen, Oak Terrace, Minnesota, and Dr. Orin J. Farness, Tucson, Arizona, will be pleased to receive recommendations from members of the College for officers to be elected at the coming annual meeting.

There is a great deal of enthusiasm among our members throughout the world regarding the Fifth International Congress to be held in Tokyo, Japan, September 7-11, 1958. The Congress is being presented under the Patronage of the Government of Japan with Prime Minister Nobusuke Kishi as the Honorary President. The College chapters in Japan, Hong Kong, the Philippines and Hawaii are planning special scientific and social programs in connection with the Congress in Tokyo. If you are planning to attend and have not yet made arrangements, I strongly urge you to communicate with the Executive Offices of the College in Chicago and they will be pleased to assist you.

Burgess L. Gordon

SEVENTH INTERNATIONAL CONGRESS ON BRONCHOESOPHAGOLOGY

The *International Bronchoesophagological Society* will hold its Seventh International Congress in Kyoto, Japan, September 12-14, 1958, immediately following the Fifth International Congress on Diseases of the Chest in Tokyo, September 7-11. A group of physicians and their families attending the Tokyo congress will travel to Kyoto to attend the Bronchoesophagological Congress. A number of prominent physicians will participate in the scientific program at the Kyoto meeting. The preliminary program is as follows:

September 12—President's Reception (8:00 p.m.)
September 13—Morning Scientific Session
Luncheon by courtesy of the Mayor of Kyoto and the Prefectural Governor
Afternoon sightseeing tour
Banquet (7:00 p.m.)
September 14—Morning Scientific Session
Luncheon by courtesy of the Mayor of Nara and the Prefectural Governor
Sightseeing tour of Nara
Farewell Party by the President of the Congress in Kyoto

There will also be entertainment for the members and their ladies including the Kyoto Dancing Girls, pottery making, a visit to a brocade factory, deer calling, shooting the rapids, and other features characteristic of Kyoto and Nara.

For registration and further information please address Dr. Chevalier L. Jackson, Executive Secretary-Treasurer, International Bronchoesophagological Society, 3401 North Broad Street, Philadelphia, Pennsylvania.

College Chapter News

ALABAMA CHAPTER

The Alabama Chapter will hold its annual meeting in Montgomery just prior to the meeting of the Alabama Medical Society, April 17-19. The chapter meeting will be held at the Whitley Hotel, starting at 2:30 p.m. on Wednesday, April 16, and the following program will be presented:

Chairman: Arthur Calix, Decatur
"Pulmonary Emphysema, Modern Concepts Relative to Its Diagnosis and Treatment of this Disabling Disease"
Ben Branscomb, Birmingham
"Cardiac Arrest as a Complicating Factor in the Performance of Major Surgery"
Rex Perkins, Birmingham
"Byssinosis, A Review of the Literature Pertaining to This Disease Commonly Found in Residents of Alabama"
William J. Talley, Gadsden
"The Treatment of Cardiospasm"
David H. Waterman, Knoxville, Tennessee

A social hour will be held at the Whitley Hotel from 5:00 to 6:00 p.m. by courtesy of the Durr Drug Company.

CALIFORNIA CHAPTER

The California Chapter will hold its annual meeting at the Ambassador Hotel, Los Angeles, on April 26, in conjunction with the California Medical Association meeting, April 27-30.

GEORGIA CHAPTER

The annual meeting of the Georgia Chapter of the College will be held in conjunction with the annual meeting of the Georgia Medical Association on Tuesday, April 29, at the Macon Auditorium, Macon, Georgia. The guest speaker will be Dr. Paul T. Chapman, Detroit, Michigan, Director of the Tuberculosis Division, Herman Kiefer Hospital. Dr. Chapman will speak on "Acute Suppuration and Tuberculosis" at 10:30 a.m. Following Dr. Chapman's lecture, a luncheon and business meeting of the Chapter will be held in the S & S Cafeteria in Macon.

ILLINOIS CHAPTER

The Illinois Chapter of the College will hold a joint meeting with the Illinois Trudeau Society at the Faust Hotel, Rockford, Illinois on April 24.

LOUISIANA CHAPTER

The Louisiana Chapter of the College will hold its semi-annual (spring) meeting on April 12 at the Bellemont Motel, Baton Rouge. The scientific program is as follows, opening at 2:00 p.m.

Panel I—The Diagnosis and Management of Congenital Heart Disease
Moderator: Richard Fowler, New Orleans
Panelists: Page Acree, Baton Rouge
John Stotler, Baton Rouge
David Van Gelder, Baton Rouge

Panel II—Obstructive Diseases of the Esophagus
Moderator: Charles Beskin, Baton Rouge
Panelists: R. C. Boyer, Baton Rouge
Louis Ochs, New Orleans
Dennis Rosenberg, New Orleans

Panel III—Granulomatous Diseases of the Lung
Moderator: Dwight Danburg, Baton Rouge
Panelists: Walter McCook, Shreveport
Albert McQuown, Baton Rouge
John Seabury, New Orleans

5:00 p.m.—Business Meeting
6:00 p.m.—"Dutch Treat" Buffet Supper

PACIFIC NORTHWEST CHAPTER

The following officers were elected at the annual meeting of the Pacific Northwest Chapter held in Portland, Oregon, November 8-9, 1957:

President:	William G. Trapp, Vancouver, B. C., Canada
Vice-President:	Kenneth A. Tyler, Gooding, Idaho
Secretary-Treasurer:	Donald A. Campbell, Tranquille, B. C., Canada

TENNESSEE CHAPTER

The Tennessee Chapter of the College will hold its annual meeting at the Riverside Hotel, Chattanooga, on Monday, April 21. The meeting will open with a luncheon at 12:00 noon, to be followed by a business meeting at 1:00 p.m. The scientific program is as follows:

"Bronchial Adenoma"
John Carter, Chattanooga

"Problems and Pitfalls in Selection of Patients for Cardiac Surgery"
Frank London, Knoxville

"Cardiospasm"
David H. Waterman, Sheldon E. Domm, and William K. Rogers, Knoxville

"Blood Loss in Surgery"
J. C. Lougheed, Memphis

"Dehisence of the Diaphragm Associated with Fractures of the Pelvis or Lumbar Spine Due to Non-Penetrating Wounds of the Chest and the Abdomen"
R. I. Carlson, W. G. Gobbel Jr., Walter L. Diveley, and R. A. Daniel Jr., Nashville

"Pulmonary Embolism"
Ira T. Johnson, Hollis E. Johnson, and Thomas B. Holton, Nashville

"Case Presentations with X-Ray Records"
John M. Crowell, Chattanooga

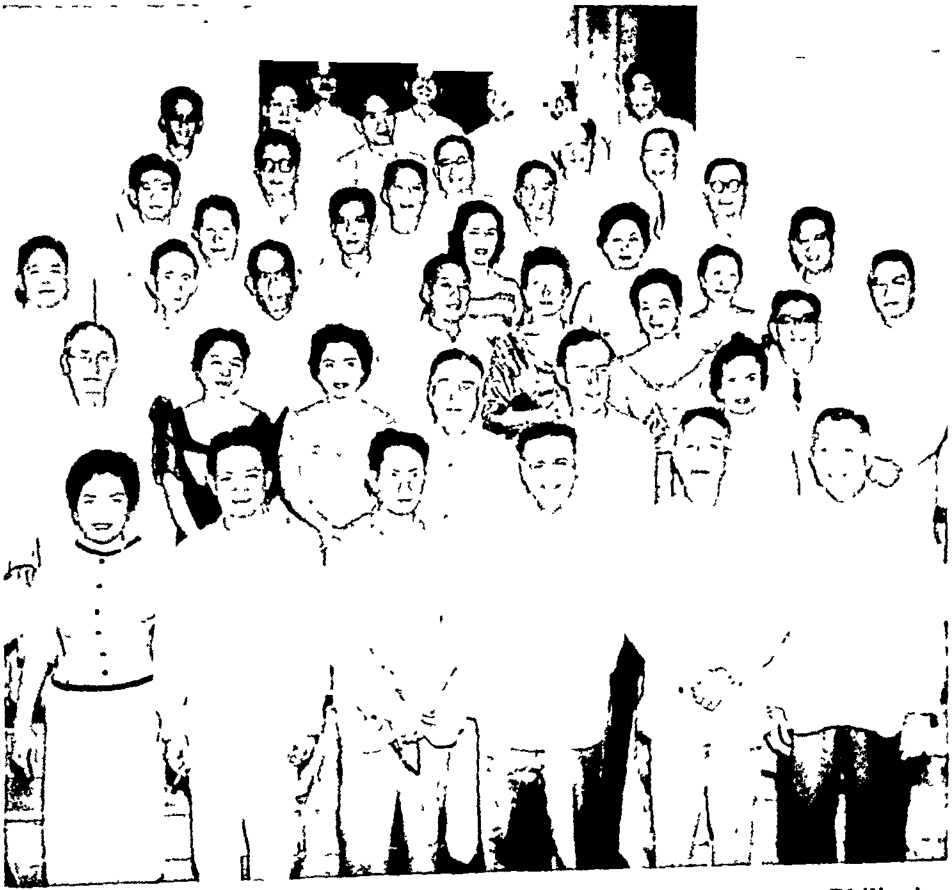
MISSOURI CHAPTER

The Missouri Chapter will hold its annual meeting at a luncheon on Sunday, April 13, at the Statler Hotel, St. Louis. Dr. Duane Carr, Memphis, Tennessee, will be guest speaker.

PHILIPPINE CHAPTER

The Philippine Chapter of the College held a special dinner meeting at the Club Filipino in Manila on November 2, 1957, during the visit of Mr. and Mrs. Murray Kornfeld (see photograph). Mr. Kornfeld addressed the meeting on the subject "The College as an International Force in the Interests of Science and World Peace." Approximately 100 members of the College in the Philippine Islands attended this special meeting. Plans for the attendance of a large delegation of members from the Philippines to the Congress in Tokyo next September were discussed and it is also planned to have a post-congress meeting in Manila, sponsored by the Philippine Chapter of the College. Dr. Miguel Canizares, Regent of the College for the Philippines, will be in charge of the arrangements.

While in Manila, Mr. Kornfeld visited the Quezon Institute where a luncheon meeting was held, attended by the officers of the Philippine Chapter. He also paid his respects to Mrs. Magsaysay, the widow of the late President of the Philippine Islands.



1st Row, Left to Right: Dr. Priscilla Tablan, Secretary-Treasurer, Philippine Chapter, Dr. Godofredo Hebron, President, Philippine Chapter, Dr. Miguel Canizares, Regent for the Philippines, Mr. Murray Kornfeld, Executive Director of the College, Dr. Manuel A. Quisumbing, Governor for the Philippines, Dr. Horace de Lien, Director of Public Health Division, Mutual Security Agency, Special Technical and Economic Mission to the Philippines. *2nd Row, Left to Right:* Dr. Sixto A. Francisco, Dr. Soledad Florendo, Dr. Sofia Bona, Dr. B. Valdes, Dr. B. Canaga, Dr. In. P. de Tavera.

BARCELONA (SPAIN) CHAPTER

The Barcelona Chapter of the American College of Chest Physicians will hold a scientific meeting in Zaragoza, March 31-April 1, 1958. All physicians are cordially invited to attend.

TEXAS CHAPTER

The annual meeting of the Texas Chapter will be held in Houston on April 20, in conjunction with the Texas State Medical Association meeting, April 20-23. The following program will be presented.

9:00 a.m. Lawrence M. Shefts, San Antonio, presiding
"Bronchogenic Carcinoma in Routine Tuberculosis Hospital Admissions"
Ellison F. White, Harlingen, and Carlos J. Quintanilla, San Antonio
"Observations on Quarantine Patients"
James P. Hodges, San Antonio
"Fungus Skin Testing of Routine Admissions to a Tuberculosis Hospital"
Edmund Rague, Kerrville
"Allergic and Toxic Reactions of Prolonged Chemotherapy for Pulmonary Tuberculosis"
Bernard T. Fein, San Antonio
Panel Discussion on "Treatment of Tuberculosis"
David McCullough, San Antonio, Moderator
A. Wilson Harrison, Galveston
Lloyd R. Hershberger, San Angelo
John W. Middleton, Galveston
Jack Miller, Galveston
Samuel Topperman, Tyler

12:30 p.m. Luncheon and Business Meeting
Remarks: Burgess L. Gordon, Albuquerque, New Mexico President, American College of Chest Physicians

2:00 p.m. John A. Wiggins, Ft. Worth, presiding
Charles M. Hendricks Memorial Lecture
"The Problems of Chronic Pulmonary Conditions in Older People"
Burgess L. Gordon, Albuquerque, New Mexico
"Mediastinal Tumors"
J. Walter Park III, San Antonio
"Ivalon Sponge Plombage and Prosthesis"
James E. Dailey, Houston
"Resection for Pulmonary Tuberculosis in Patients Over 50 Years of Age"
Clyde E. Rush, Sanatorium

ARGENTINE CHAPTER

The Argentine Chapter of the College met in Concordia on November 10, 1957. The themes discussed were "Treatment of Pulmonary Suppurations" (Non-tuberculous with the exception of bronchiectasis) and "The Use of the Corticosteroids and ACTH in the Treatment of Tuberculosis." Following the scientific session, the following officers were elected:

President:	Oscar Izaguirre, Parana
Vice-President:	Isaac Wolaj, Cordoba
Secretary-Treasurer:	Enrique C. R. Bonfils, Parana

CANARY ISLANDS (SPAIN) CHAPTER ORGANIZED

On November 2, 1957, the Canary Islands Chapter of the College was officially organized during a meeting held by the Barcelona Chapter in Palma de Mallorca. The following officers were elected:

President:	Camilo Rodriquez Gavilanes, Las Palmas
Vice-President:	Jose M. del Arco Montesinos, Sta. Cruz de la Palma
Secretary:	Santiago Enrique Gonzalez, La Laguna
Treasurer:	Jose J. Perez Perez, Sta. Cruz de Tenerife

Arrangements for the meeting were made by Dr. Antonio Caralps, Barcelona, Regent of the College, and Dr. Tomas Cervia, Tenerife, Governor of the College for the Canary Islands.

PENNSYLVANIA CHAPTER

The Pennsylvania Chapter of the College will hold a *Clinical* Session at the Reading Hospital, Reading on Wednesday, April 16. The following program will be presented:

10:30 a.m. "Shall We Treat the Tuberculin Converter?"
David A. Cooper, Philadelphia
Discussor: John H. Bisbing, Reading
Report of the 17th VA-Armed Forces Conference on Chemotherapy of Tuberculosis
Carl W. Tempel, Valley Forge
"An Evaluation of Chemotherapy in Pulmonary Tuberculosis; High Doses of INH with PAS and Pyridoxine"
Stephen J. Berte, Valley Forge
Discussor: Robert L. Mayock, Philadelphia
"Progress in the Diagnosis of Left Heart Lesions"
Don Fisher, Pittsburgh
Discussor: Gordon Myers, Harrisburg
1:00 p.m. Luncheon
2:00 p.m. "The Surgical Management of Pulmonary Emphysema"
John M. Snyder, Bethlehem
Discussor: William DeMuth, Carlisle
"Pulmonary Embolism as a Cause of Massive Pleural Effusion"
Albert L. Sheffer, Dick D. Harrell and Harold L. Israel, Philadelphia
Discussor: Katharine R. Boucot, Philadelphia
"Complacency Concerning Chest Diseases"
Howard Witmer, Lancaster

OHIO CHAPTER

The annual meeting of the Ohio Chapter will be held at the Netherland Plaza Hotel, Cincinnati, on Wednesday, April 16.

PANAMA CHAPTER ORGANIZED

The organizational meeting of the Panama Chapter of the College was held in Panama City on February 13. Dr. Maximo Carrizo Villarreal, Colon, serves as Regent of the College for Panama and Dr. Rodolfo V. Young, is Governor. The following chapter officers were elected:

President:	Alberto Calvo, Panama City
Vice-President:	Octavio Ferrari Jr., Panama City
Secretary-Treasurer:	Antoine Raymundo, Panama City

College News Notes

Dr. Jerome R. Head, Chicago, Illinois spoke on "Philosophy and Medicine" on February 25 in Northwestern *University Medical School's lecture series on* "The Growth of Medicine" at the medical school.

Dr. Milton M. Hurwitz, St. Paul, Minnesota, was recently elected President of the Minnesota Heart Association.

The following members of the College have recently been certified in the Sub-specialty of Pulmonary Diseases by the American Board of Internal Medicine; **Dr. Virgil A. Plessinger**, Cincinnati, Ohio; **Dr. Edgar A. Riley**, New York City; **Dr. Gordon L. Snider**, Chicago, Illinois. **Dr. W. W. Coulter, Jr.**, of Lafayette, Louisiana, has received his certificate in Internal Medicine.

Dr. Oglesby Paul, Chicago, Illinois lectured on "Diet and Diuretics in Congestive Heart Failure" at St. Mary of Nazareth Hospital, Chicago, January 3.

Dr. Roscoe C. Giles, Assistant Professor of Surgery at Chicago Medical School was a recipient of the citation given as outstanding Chicago citizen by the Jesuit Centennial Committee on December 12.

Dr. Harry Isaacs was honored at a dinner on November 30, initiated by members of the Department of Medicine at Chicago Medical School in recognition of his retirement as head of that department.

Dr. H. C. Jernigan, director at large, National Tuberculosis Association Board of Directors has been appointed medical director of the Fort Staunton Tuberculosis Hospital, Fort Staunton, New Mexico.

Dr. Clare Miller, Medical Director of Hillcrest Sanatorium, Quincy, Illinois for the past 27 years, resigned in October.

Dr. George E. Burch, New Orleans, Louisiana, was an out-of-state speaker at the 10th Annual Clinical Assembly of the Arkansas Chapter of the American Academy of General Practice at Little Rock, Arkansas, October 16-17, 1957.

Brigadier General Carl W. Tempel, U. S. Army, Commanding General of Valley Forge Army Hospital, Phoenixville, Pennsylvania, was one of six medical leaders who were honored by the Association of Military Surgeons of the United States at its meeting in Washington, D. C., October 30, 1957.

Dr. Howard F. Root, Boston, Massachusetts, was an out-of-state speaker at the 9th Annual Scientific Assembly of the Maryland Academy of General Practice at Easton, Maryland, October 9-10, 1957.

Dr. Paul Dudley White, Boston, Massachusetts, was a speaker at the 9th Annual Symposium on Heart Disease sponsored by the Washington State Department of Health and the Washington State Heart Association, held at Seattle, October 4-5, 1957.

Dr. George F. Evans, Clarksburg, West Virginia, was named Vice President of the West Virginia State Medical Association at its recent annual meeting held at White Sulphur Springs.

Dr. Charles E. Lyght, Rahway, New Jersey, Director of Medical Publications, Merck Sharp & Dohme Research Laboratories, was recently elected President for 1958 of the American Medical Writers Association.

Dr. Claude S. Beck, Sr., Cleveland, spoke on "Trends in the Surgical Treatment of Coronary Artery Disease" at a professional symposium sponsored by the Gaston County Heart Association, February 3.

Dr. Alton Ochsner, New Orleans, Louisiana, will speak on "Carcinoma of the Lung" at the Chicago Medical Society Clinical Conference at the Palmer House, Chicago, Illinois, March 4-7.

Drs. Leo G. Rigler, Los Angeles California and **Sol Katz,** Washington, D. C., will serve on a panel on diagnostic x-ray functions at the American Academy of General Practice 1958 Scientific Assembly program March 26.

Dr. Eugene T. McEnery, Chicago is the Chairman of the Annual Conference sponsored by the Chicago Medical Society at the Palmer House March 4-7.

Book Reviews

SYMPOSIUM—THE MANAGEMENT OF TUBERCULOSIS, Irving J. Selikoff, Editor. Waverly Press, Baltimore, 1956.

A praiseworthy project of the Journal of the Mount Sinai Hospital materialized when it carried a symposium on the management of tuberculosis in its July-August 1956 issue. Written by members of the Mount Sinai Hospital of New York City and published in book form by the Waverly Press, this work represents an important contribution to current medical literature. It contains a remarkably thorough and competent assaying of modern chemotherapy of this disease, with special attention to problems of pertinent interest, including combination of various antimicrobial agents and occurrence of tubercle bacilli resistant to specific drugs. The data offered are based on extensive clinical material and carry the hallmark of keen observation, and discriminating, prudent judgment. Emphasis on certain therapeutic precepts are derived from personal experience of the authors and augmented by corroborative references. Ample space devoted to the discussion of respiratory function studies, tuberculous pleurisy with effusion, tuberculosis in childhood and pulmonary resection. Other topics which are adequately covered include tuberculous meningitis and lymphadenitis, moreover, genito-urinary, cutaneous and orthopedic forms of tuberculosis. Impressive chapters deal with tuberculoma of the lung, tuberculosis of the larynx and intestines, pregnancy and tuberculosis as well as diabetes and tuberculosis. Discussion of the rehabilitation of the tuberculous patient renders the text a truly comprehensive assay. The book has a pleasing format. It is printed on excellent paper and is enriched with illustrations of technical precision and of highly instructive value.

Andrew L. Banyai, M.D.

EAR, NOSE AND THROAT DYSFUNCTIONS DUE TO DEFICIENCIES AND IMBALANCES. By Dr. Sam E. Roberts. Springfield, Illinois: Charles C Thomas, 1957. Pp. 323, 58 figures. Price: $8.50.

Dr. Morris Fishbein, who contributed the foreword to this book, was impressed by the fact that "Dr. Roberts has wisely recognized that conditions affecting the nose, throat, the sinuses, the nervous system—in fact, any portion of the human body—are in a sense not localized but constitutional disorders. Obviously the attack on a constitutional disorder is not limited to surgical correction of the anatomical errors nor to elimination of infectious or toxic agents. The attack must be total." Dr. Roberts states: "I am certain that deficiencies, and especially imbalances, are the principle causes of the diseases, dysfunctions and syndromes herein reported." In considering such areas of otolaryngological interest as headaches, Meniere's disease, perceptive hearing loss, sore throat, sinus dysfunction and allergy, the author attempts to associate accepted facts concerning metabolic disturbances and nutritional deficiencies with the presenting symptoms of the patients he has observed in almost a half century of practice. By the employment of numerous historic forms the patient indulges in a self analysis of his diet, his habits, his symptoms and other personal historical facts by checking "yes" or "no."

Dr. Roberts has likewise systematized instructions to the allergic patient and specific and general nutritional orders and suggestions on cards prepared for distribution to the patient. Each area of discussion, including those already mentioned, and gonadal, and insulin-sugar imbalances, are supported by case reports to substantiate the author's contention that metabolic disturbances and nutritional deficiencies may affect the ear, nose and throat. He seeks to establish the accepted thesis in this regard by a large number of hypotheses and speculations which he believes to "represent sound basic tenets."

Francis L. Lederer, M.D.

SYMPOSIUM ON TUBERCULOSIS. Edited by F. R. G. Heaf, London, 1957. 755 and xvi pages. 78 plates. 54 figures. 110 tables. 1200 references.

This comprehensive volume by more than a dozen leading British authorities, presents a picture of tuberculosis in England strikingly different from that in the United States today.

Tuberculosis is regarded as a universal infection, its manifestations depending chiefly on differences in resistance of the victims, bovine type infections and extrapulmonary forms accounting for a large part of the morbidity. Diagnosis is chiefly history, physical examination and x-ray, among persons coming in because of symptoms, and treatment is chiefly the collapse therapy, medical and surgical, and chemotherapy with the three drugs, streptomycin, PAS, and INH, with rehabilitation efforts aimed at early return to work, sometimes even while still sputum positive.

In America, where less than 10 per cent of the population under 25 have been infected, 80 per cent of those dying of tuberculosis are over 45 years of age, the importance of frequency and dosage of infection and reinfection is stressed, bovine tuberculosis has been eradicated, and extrapulmonary tuberculosis is only an infrequent occurrence. Diagnosis is sought by routine minifilm screening of hospital admissions, prisoners, pensioners and other large groups with high incidence, and treatment relies chiefly on prolonged chemotherapy, with other agents when the standard triad fails, resection of persistent cavities, and relief from economic pressure by disability and old age pensions and other social security measures.

This contrast is overdrawn, as the authors are themselves aware of the great differences between tuberculosis in England and in the undeveloped countries, in the past and the present, and the rapidly changing picture during the past few years. The differences in epidemiological factors do not obliterate the fundamental identity of the clinical disease, clearly presented in these pages. There is much of value here in the careful conservative marshalling of facts, the objective analysis of the data, the tolerant evaluation of conflicting interpretations, the philosophic acceptance of opposition and the British persistence in the face of obstacles and setbacks.

Emil Bogen, M.D.

DISEASES of the CHEST

VOLUME XXXIII APRIL, 1958 NUMBER 4

An Aerosol Method of Producing Bronchial Secretions in Human Subjects:

A Clinical Technic for the Detection of Lung Cancer

HYLAN A. BICKERMAN, M.D., F.C.C.P., EDITH E. SPROUL, M.D.
and ALVAN L. BARACH, M.D., F.C.C.P.
New York, New York

The increasing importance of lung cancer as a major health problem has recently been emphasized by Gerhardt, Handy and Ferber[1] who compared the age-standardized incidence rates for cancer for the years 1942 and 1955 in New York State. In man, the outstanding change in incidence rates over the 14 year period was the 202 per cent increase in carcinoma of the lung and bronchus. Even more striking is the increase of 520 per cent in the death rate due to lung cancer among the male population over the past 22 years. In women, this increase was 75 per cent. Similar trends have been reported for other states and for the United States as a whole.[2]

The rising incidence of bronchogenic carcinoma makes early diagnosis a factor of vital importance. The number of patients diagnosed with lung cancer in an operable stage and with a reasonably good prognosis is still small. Lutwyche[3] in a review of 116 cases of bronchial carcinoma noted a considerable delay in diagnosis in one third of his series. At present, there is no unanimity of opinion regarding the value of chest roentgenograms in screening for early lung cancer. Opinions vary from the belief that most cases have already metastasized by the time they are suspected radiologically, to the conviction that many are still localized and resectable.[4]

Since the first report by Hampeln[5] in 1918 on the presence of malignant cells in the sputum of patients with bronchogenic carcinoma, a number of investigators[6-8] have confirmed the importance of cytologic examination in the diagnosis of lung cancer particularly in the early stages. Employing technics developed by Papanicolaou,[9] the accuracy of diagnosis by sputum cytology has ranged from 84 to 93.5 per cent in the various series published. Farber and his associates[10] reported a 90 per

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From the Columbia University Research Service, Goldwater Memorial Hospital, the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian and Francis Delafield Hospitals.

This study has been supported by the American Cancer Society.

Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.

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cent accuracy in the positive diagnosis of lung cancer when five or more sputum specimens were examined. This degree of accuracy declined sharply when fewer specimens were studied.

In formulating a screening program for the early detection of lung cancer in apparently healthy individuals, cytologic methods have been considered impractical since the vast majority of these subjects are asymptomatic and raise no sputum. An approach to this problem has been made by utilizing the principles and technic of producing sputum in human subjects by the inhalation of hypertonic saline aerosols. The preliminary results of such cytologic screening are reported in this paper.

Theoretical Considerations

The problem of depositing an aerosol on the tracheo-bronchial mucosa which would induce bronchial secretions in apparently healthy individuals and yield sputum specimens suitable for cytologic study raised certain considerations. Among the factors which determine the degree of retention of an aerosol and the sites of deposition within the respiratory tract are: particle size and density, vapor pressure, temperature and hygroscopic properties of the aerosol, and the rate and depth of respiration. Findeisin[11] showed that 97 per cent of solid particles of 1 micron radius and above are deposited within the lung. Particles of 3 micra in radius are taken out completely by the trachea, bronchi and bronchioles. The retention of aerosol droplets in the human respiratory tract as a function of particle radius and respiratory rate was studied by Wilson and La Mer.[12] A maximal retention of approximately 50 per cent occurred in the alveoli and bronchioles with particles of 1.0 micron in radius. The stability of a water droplet 0.5 micron in radius under ordinary conditions of humidity is only a fraction of a second due to its high evaporation rate. Furthermore, rapid absorption of isotonic aerosols took place within the tracheobronchial tree. Studies by Abramson[13] indicate that droplet evaporation is decreased with aerosols in a glycerin solution because of the reduction in vapor pressure, serving to stabilize the aerosol mist.

TABLE I
AGE AND SEX DISTRIBUTION OF 336 PATIENTS RECEIVING HYPERTONIC SALINE AEROSOLS

Groups*	Sex	Number of Subjects	Age Mean (Years)	Age Range
A	Male	125	55.3	21-90
	Female	78	53.1	18-86
B	Male	75	59.3	35-78
	Female	35	44.3	20-73
C	Male	20	58.9	30-75
	Female	3	51.0	50-52

*A—No evidence of pulmonary pathology
B—Chronic non-tuberculous pulmonary disease
C—Known or suspected malignancy

Using aerosols containing radioactive solium, Talbot, Quimby and Barach[14] found that the addition of 10 per cent propylene glycol to the aerosol solution results in a greater deposition within the lung than is produced by isotonic mists. Barach, Garthwaite and Bickerman[15] noted that the comfort of inhaling penicillin aerosols is enhanced by providing a warm aerosol, and in addition, higher blood levels are obtained as compared with cold aerosols indicating an increased deposition of the penicillin mist.

The osmotic effect of hypertonic saline solutions for the purpose of this project was suggested by a study of Barach, Mason and Jones[16] who noted a marked and instantaneous increase in plasma volume following the intravenous administration of 100 ml. of 15 per cent saline solution. It seemed likely that the impingement of an adequate number of hypertonic saline droplets upon the bronchial mucosa would, osmotically, induce transudation. Such a bronchial transudate might then wash exfoliating cells from the regions of aerosol deposition into the material subsequently expectorated.

Methods

With the above considerations in mind, various concentrations of saline solution ranging from 3 to 15 per cent were employed to induce sputum production. A 10 per cent sodium chloride solution has been used in the majority of instances since the incidence of irritation appeared to be less than with the 15 per cent concentration. It was necessary to limit the saline aerosol to 3 per cent in some patients with bronchial asthma and pulmonary emphysema since the more hypertonic solutions appeared to accentuate obstructive dyspnea. Initially, 40 per cent propylene glycol

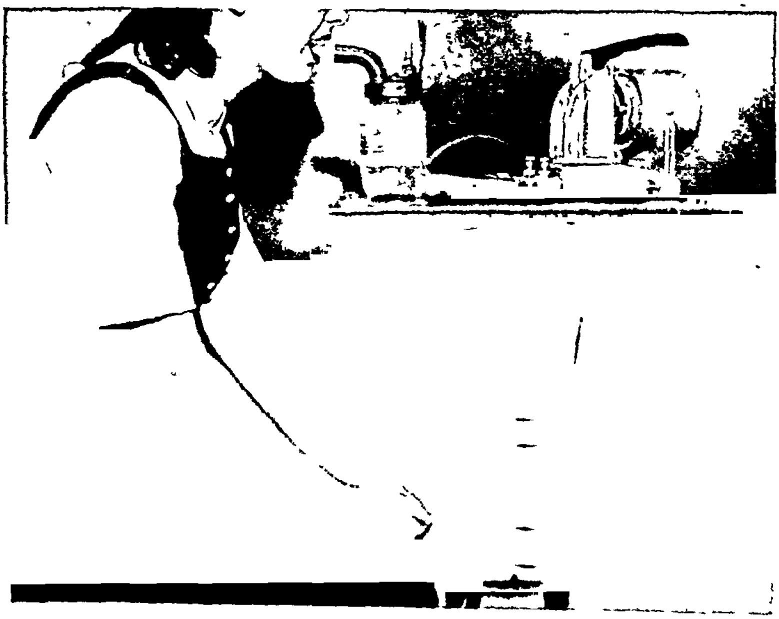

FIGURE 1: Photograph illustrating the inhalation of warm hypertonic saline aerosol generated in a high flow nebulizer by means of an air pump.

was employed but this hygroscopic aerosol was too viscid and often occluded the nebulizer. The addition of 15 or 20 per cent propylene glycol to the saline solution provided a stable mist which did not usually interfere with continuous nebulization.

Since nebulization of a large quantity of aerosol solution within a limited period of 10 to 20 minutes appeared desirable, high-flow nebulizers which produced a relatively large particle size ranging between 1 to 10 micra in radius were employed. A small pump producing an air-flow of 5 to 7 liters per minute through the nebulizer generated the aerosol mist. Since initial studies had clearly shown that irritation was reduced and the comfort of inhalation enhanced by warming the aerosol, the solution within the nebulizer was heated by placing the reservoir of the nebulizer over a steam generator or electric coffee percolator.* The nebulizers originally employed included a large capacity baffle-less Vaponefrin nebulizer** and the Aero-Mist nebulizer.† More recently, a high-flow nebulizer‡ has been developed which nebulizes 1 ml. of hypertonic saline per minute, and incorporates a thermostatically controlled heating unit adjusted so as to provide an aerosol warmed to 105° to 130° C. A photograph and line drawing of this nebulizer are illustrated in Figures 1 and 2.

Procedure

A total of 336 patients from the wards of the Goldwater Memorial Hospital, Francis Delafield Hospital and the Asthma Clinic of the Co-

TABLE II

THE RECOVERY OF SPUTUM IN 336 SUBJECTS FOLLOWING THE INHALATION OF HYPERTONIC (10 AND 15 PER CENT) SALINE AEROSOLS

		Results		
		Positive**		*Negative*
Group	Number of Subjects	Number	Per Cent	Number
A-I	180	155	86.1	25
II	23	0	0	23
B	110	99	90.0	11
C	23	23	100.0	0
TOTAL	336	277	82.5	59
Corr. Total (*excl.* A-II)	313	277	88.5	36

*A—No pulmonary pathology (A-II pts. with *impaired cough reflex*)
B—Chronic non-tuberculous pulmonary disease
C—Suspected malignancy
**mucoid sputum exceeding 1 ml.

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*West-Bend Aluminum Co., West Bend, Wisconsin.

**Manufactured by Vaponefrin Co., Upper Darby, Pennsylvania.

†Obtained from Medical Specialties, Inc., Boonton, New Jersey.

‡Manufactured by O. E. M. Corp., East Norwalk, Connecticut. Homemakers' Products Corp. manufactures an inexpensive, *effective* apparatus providing the higher temperatures now generally employed.

lumbia-Presbyterian Medical Center participated in the study. They were divided into three groups:

Group A: This group consisted of 203 patients with a wide variety of illnesses but with no evidence of pulmonary disease by clinical and roentgenologic study. These individuals were classified as apparently healthy with respect to the respiratory system and had no cough or spontaneous sputum.

Group B: This group consisted of 110 patients with chronic non-tuberculous pulmonary disease in whom the diagnosis of bronchial asthma, pulmonary emphysema and chronic bronchitis predominated.

Group C: This group consisted of 23 patients with known or suspected malignancy involving the lung or other organs. These patients were selected in such a manner that neither the technician who performed the test nor the pathologist who examined the sputum were aware of the diagnosis. Certain statistics for each of the three groups are shown in Table I.

Each subject inhaled the warmed aerosol produced by the continuous nebulization of a solution containing 10 or 15 per cent sodium chloride and 20 per cent propylene glycol for periods of 10 to 20 minutes. Because of an increased incidence in wheezing and coughing among the patients in Group B with bronchopulmonary pathology, the salt content of the aerosol was subsequently lowered to 3 per cent, as mentioned above, and was often preceded by an inhalation of 0.2 ml. of 2.25 per cent racemic

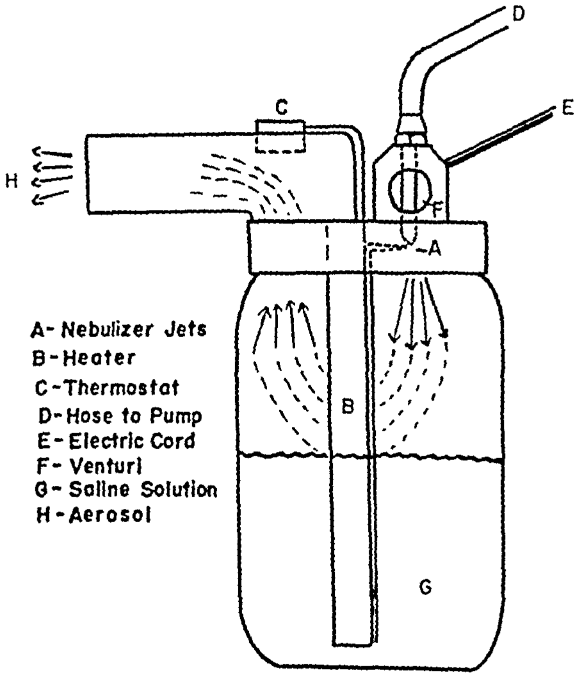

FIGURE 2: Line drawing of high-flow nebulizers with a thermostatically controlled heating element. Aerosol particle size ranges between 1 to 10μ in radius.

epinephrine (Vaponefrin)* or 0.4 per cent isuprel.** The latter procedure was followed in the last 20 patients of this group. All of the material expectorated during, and for 10 minutes following the aerosol inhalation was collected and measured. Gross appearance with respect to color, consistency and the presence of mucoid or muco-purulent shreds or plugs were noted. The recovery of mucoid material exceeding 1 ml. in amount indicated, in our opinion, that the specimen had been obtained from the tracheo-bronchial passageway since it could readily be distinguished from saliva, especially after the expectorated material was added to an equal volume of 70 per cent ethyl alcohol.

Spontaneous sputum collections were performed on 16 patients with chronic bronchitis prior to aerosol therapy. Each subject was then given an inhalation of 10 per cent sodium chloride and 20 per cent propylene glycol. Specimens obtained prior to the aerosol and after the inhalation of the hypertonic saline solution were analyzed quantitatively for total chloride content.

Sputum specimens following aerosol therapy were collected from 74 subjects including 19 patients with suspected malignancy, placed in an equal volume of 70 per cent ethyl alcohol and processed for cytologic study.

Results

Following the inhalation of hypertonic saline aerosols, specimens of sputa were obtained from 277 of the 336 patients treated. This is illustrated in Table II. Initially it was observed that 76.4 per cent of the patients in Group A yielded sputum specimens whereas 90 per cent of the patients with pulmonary disease and 100 per cent of the group with suspected malignancy raised adequate sputum samples. On further examination of the negative responders in Group A, it was found that 23 of these

TABLE III

DURATION OF INHALATION AND AMOUNT OF AEROSOL ADMINISTERED TO 277 SUBJECTS WITH RECOVERABLE SPUTUM

Groups*	No. of Subjects	Per Cent Concentration Saline Aerosol	Means Aerosol Admin. Amount (Ml.)	Means Aerosol Admin. Time (Ml.)	Sputum Collected (Ml.)
A	155	10 or 15	7.7	15.0	5.7
B-I	79	10	9.2	12.0	8.0
II	20	3	8.8	11.7	8.0
C	23	10	10.3	13.0	7.2

*A—No pulmonary pathology
B—Chronic non-tuberculous pulmonary disease
(B-II—asthmatics receiving 3 per cent saline)
C—*Suspected malignancy*

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* Vaponefrin Co., Upper Darby, Pa.

** Isoproterenol, 0.4 per cent, was mixed with phenylephrine 2.0 per cent, supplied as a Nebu-Isophrin by Homemakers' Products Corporation, Englewood Cliffs, New Jersey.

patients had neurologic disorders with marked impairment of the cough mechanism. These included 16 patients with hemiplegia, three with poliomyelitis, two with muscular dystrophy and two with meningovascular syphilis. Correcting the data by excluding these individuals, (Group A-II), resulted in an 86.1 per cent recovery of sputum from patients in Group A and an 88.5 per cent recovery for the combined series.

The amount of aerosol administered and the duration of each treatment were roughly comparable in all three groups. This is illustrated in Table III. Minor variations were related to the different nebulizers and aerosol pumps employed in the early phases of the study. Although the amount of sputum recovered varied widely from subject to subject, in general, those in Groups B and C gave higher yields than the subjects with no apparent pulmonary pathology. It must be recognized that the amount of sputum collected was at best a rough estimate since admixture with saliva and aerosol made quantitative measurement impossible. Nevertheless a sufficient amount of material was available in almost every instance for cytologic study.

Preliminary studies with cold hypertonic saline areosols resulted in frequent complaints of a sense of irritation to the upper respiratory tract as manifested by scratchiness of the throat, hoarseness and cough. This was materially reduced when the aerosols were warmed to 40 to 44° C.

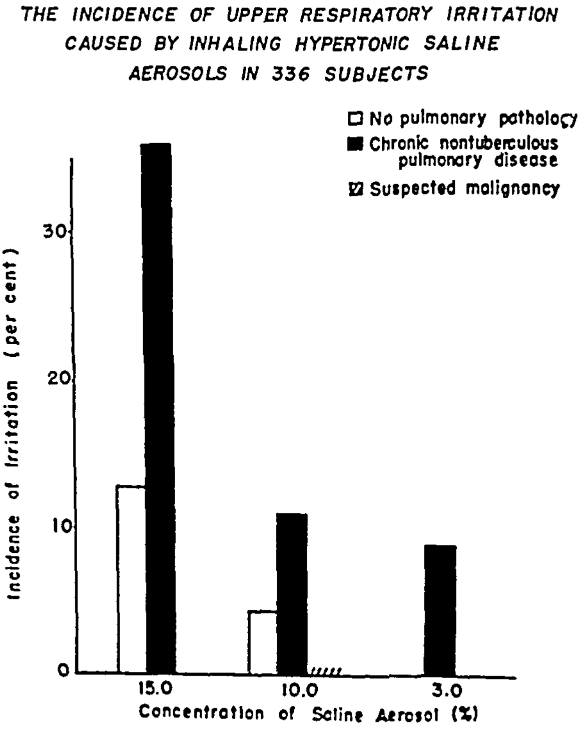

FIGURE 3: The incidence of upper respiratory irritation caused by inhaling hypertonic saline aerosols in 336 subjects, illustrating a positive correlation between the concentration of saline and per cent increase in irritation.

The incidence of upper respiratory irritation for the warmed aerosols is illustrated in Figure 3. Only 10 per cent saline solutions were employed in the patients with suspected malignacy and none of these reported any irritative symptoms. It is evident that a positive correlation exists between the incidence of irritation and the degree of hypertonicity of the saline aerosol. As might be expected, the per cent of subjects experiencing irritation was higher for those in Group B with asthma and pulmonary emphysema than for the subjects in Group A when either 10 or 15 per cent saline was inhaled. With a warmed 10 per cent saline aerosol, only three (4.3 per cent) in Group A, with no evidence of pulmonary pathology, complained of irritation.

A comparison of the total chloride content of the sputum collected on 16 subjects in Group B before and after administering an average of 8 ml. of 10 per cent saline aerosol showed a slight but insignificant increase in the chloride content of the sputum following the inhalation of the hypertonic saline solution. This is illustrated in Table IV. These findings would appear to indicate an osmotic effect resulting in the rapid dilution of the hypertonic aerosol droplets by bronchial transudate.

Cytologic Studies

Sputum specimens obtained from 74 subjects following inhalations of 10 per cent saline aerosol were subjected to cytologic study. Since material was recovered from patients with a variety of pulmonary disorders as well as from individuals free of lung disease, the character of the specimens varied greatly. In general, the induced sputum of "normal" individuals contained little gross particulate matter and appeared pale, whereas specimens from patients with pulmonary pathology appeared more mucoid and in some instances contained fresh muco-purulent plugs.

1. Method of Processing Specimen: The specimens arrived in the laboratory in glass bottles containing equal volumes of 70 per cent alcohol which had been added to the material expectorated. The entire contents were centrifuged for 15 minutes at 1500 rpm and the supernatant fluid decanted. The superficial part of the sediment was transferred to glass slides with a small spatula and two to four smears were prepared. Routine preparation included one hematoxylin-eosin and one mucicarmine

TABLE IV

COMPARISON OF THE CHLORIDE CONTENT OF THE SPUTUM COLLECTED FROM 16 PATIENTS BEFORE AND AFTER INHALING 10 PER CENT SALINE AEROSOL

	Number of Subjects	Mean Amount Sputum (ml.)	Mean Chloride Content	
			Mgs. Per Cent	S. D.
Before Aerosol	16	3.8	197.0	72.0
—mean of 8.3 ml. 10 per cent saline aerosol administered—				
After Aerosol	16	6.4	244.7	80.8

stain. The remainder of the sediment was fixed in Bouin's solution, embedded in paraffin in the autotechnicon and sectioned. At least one hematoxylin-eosin and one mucicarmine stained slide were routinely prepared.

II. Cytologic Observations: a) Preservation of cells: No distortion of cells which might be attributed to hypertonic saline were observed. There was no shrinkage or crenation. The nucleus and cytoplasm seem to be preserved in relative proportion. Nuclear chromatin pattern was distinct and the granular or vacuolar character of the cytoplasm was maintained. The cells did not appear altered as compared with their spontaneously ejected counterparts. Variation in cell preservation and staining qualities could be attributed to the vicissitudes of the autotechnicon and technician.

b) Cell types: Sixteen of the 74 specimens contained only superficial squamous cells and leukocytes. These were regarded as unsatisfactory for study since there was no evidence that any of the material came from the lower respiratory tract. Most sediments contained alveolar phagocytes with anthracotic pigment and rarely some hemosiderin or fat vacuoles. The phagocytes varied in numbers about as one would expect from different individuals. Even healthy subjects yielded phagocytes (all were city dwellers or workers) and often in considerable quantities. The presence of these cells was regarded as an index of the depth from which the specimen was obtained since they occurred in clumps, which would be an unlikely finding if they were in the trachea or pharynx.

Bronchial epithelial cells were less numerous than alveolar phagocytes

FIGURE 4

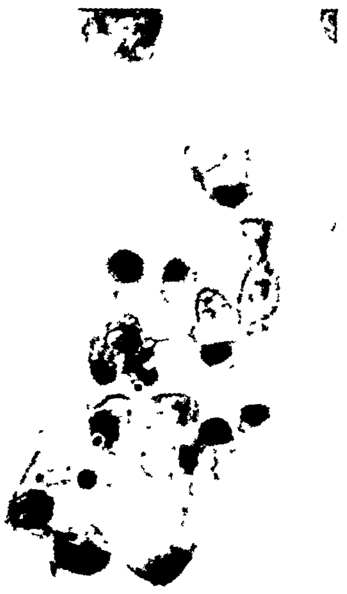

FIGURE 5

Figure 4 Photomicrograph of the sputum smear of a subject with hypertension (Group A) illustrating clusters of columnar, ciliated bronchial epithelial cells of normal character.—*Figure 5:* Smear of the sputum obtained from a patient with severe bronchial asthma (Group B) showing bronchial epithelium distended with mucus. One slender cell presents a ciliated border. This amount of mucus is abnormal

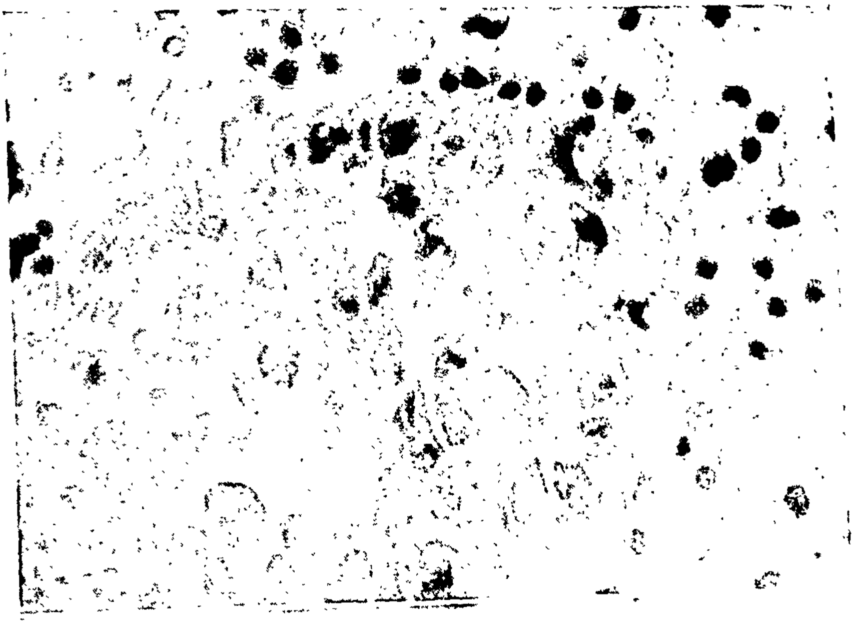

FIGURE 6

FIGURE 7

FIGURE 8

but were very well preserved. In general these cells showed less alteration than that observed in spontaneous sputum. Cilia were easily seen. This is illustrated in Figure 4. One to three nuclei with fine chromatin appeared at the apposing end of the cell and the cytoplasm was finely granular or vacuolated. The vacuoles sometimes contained mucicarminophilic material. In the material from several patients bronchial epithelium distended with mucus was abundant. The photomicrograph (Figure 5) of a smear from sputum obtained from a patient with severe bronchial asthma reveals bronchial epithelium distended with mucus. Polymorphonuclear neutrophils and lymphocytes were readily identified. Occasionally eosinophils were abundant.

The abnormal cells were not numerous, occurring in six of the specimens. None were found in material from healthy individuals. The benign abnormalities took the form of strips of cuboidal cells resembling swollen alveolar lining cells such as one sees about the air spaces in a lung with thickening of the alveolar walls. There were also cuboidal squamous cells with relatively large nuclei resembling parabasal cells which may have represented squamous metaplasia in the bronchial tree. In this series, cancer appeared only as squamous carcinoma. The malignant cells occurred individually and in clumps. One patient produced pieces of cohesive tumor cells. Figures 6 and 7 show squamous carcinoma cells from the cell block and smear respectively on sputum recovered from a patient with known squamous cell carcinoma of the lung. A cluster of malignant cells is illustrated in Figure 8 recovered in the sputum of a patient with epidermoid carcinoma of the lung.

TABLE V

RESULTS OF CYTOLOGIC STUDIES PERFORMED ON SPUTUM RECOVERED FROM 74 SUBJECTS FOLLOWING INHALATION OF 10 PER CENT SALINE AEROSOL

		CYTOLOGIC EXAMINATION			
Group*	Number of Subjects	Positive for Malign. Cells	Abnorm. Cells Suspicious Mal.	Negative for Malign. Cells**	Unsatisfact. Specimen***
A	27			23	4
B	28			21	7
C	19	4	2	8	5
TOTAL	74	4	2	52	16

*A—No pulm. path. B—Chronic pulm. disease. C—Suspected malignancy
**Specimen contained well preserved respiratory epithelium
***insuff. quantity, no respir. epith., or purulent debris

See Figures on Opposite Page

Figure 6: A sheet of squamous carcinoma cells showing hyperchromatic nuclei, large nucleoli and mitotic figures recovered from the sputum of a patient with a known squamous cell carcinoma of the lung (Group C, cell block).—*Figure 7:* Individual malignant cells from the same patient with squamous cell carcinoma. The nuclei are relatively large, irregular and hyperchromatic with scanty cytoplasm (smear)—*Figure 8:* Cell block on the sputum recovered from a patient with epidermoid carcinoma of the left lung (Group C) showing a small cluster of malignant cells having relatively large, dark irregular nuclei and scanty cytoplasm. Several cells are degenerated.

A summary of the results of the cytologic study is shown in Table V. Fifty-eight (78.5 per cent) of the 74 specimens were judged to be representative samples of material from the lower respiratory tract satisfactory for diagnosis. Of these six from the group with suspected malignancy contained abnormal cells. Sixteen specimens were regarded as unsatisfactory for study since they contained only superficial squamous cells and leukocytes.

It was of interest to analyze the cytologic reports on the sputum obtained from the 19 patients in Group C which had been carried out in a "double-blind" fashion. This is illustrated in Table VI. Of the eight patients with documented primary or metastatic carcinoma of the lung, five of the sputum specimens induced by aerosol were positive for malignant cells. There were no false negatives in this group. Seven of the eight with malignancy in other organs not involving the lungs had no abnormal cells in their sputum, and one specimen was unsatisfactory for study. Of the sputum samples in the three patients with suspicious pulmonary infiltration on x-ray, one contained abnormal cells suggestive of squamous cell carcinoma, one was negative (subsequently diagnosed as tuberculosis) and one was unsatisfactory. Although conclusions cannot be drawn from this small series, the results of the cytologic study yielded no false positive or negative findings in those patients in whom a diagnosis had been established.

Discussion

Of the various factors which have been considered in an effective screening program for lung cancer, those of special importance include: 1) simplicity of technic, 2) non-injurious character of the procedure, 3) acceptance of the method by the subjects tested so that repeat studies are readily available, and 4) adequate criteria for establishing the diagnosis in order that the number of false positive and negative reports be minimal.

TABLE VI

ANALYSIS OF CYTOLOGIC STUDIES ON SPUTUM RECOVERED FROM 19 PATIENTS WITH KNOWN OR SUSPECTED MALIGNANCY (GROUP C) FOLLOWING INHALATION OF 10 PER CENT SALINE AEROSOL

Group C	Number of Subjects	Positive or Suspicious Mal.	Negative for Malign. Cells	Unsatisfact. Specimen*
1. Known Bronchogenic Carcinoma	7	4	0	3
2. Known Metast. Ca. to lung	1	1	0	0
3. Suspected lung cancer	3	1	1	1
4. Known or suspect. Ca. elsewhere	8	0	7	1
TOTAL	19	6	8	5

*purulent exudate predom., no respiratory epithelium seen.

The recovery of sputum adequate for cytologic study in 88.5 per cent of the combined series of 336 subjects following a single treatment with hypertonic aerosols justifies the extension of this program to a larger series. It is quite possible that negative responders might be induced to raise sputum following a second or third course of treatment with saline aerosol. Further study is required to ascertain whether conversion of these negative responders would occur with higher concentrations of saline aerosol. In addition, the effect of mechanical coughing by exsufflation with negative pressure following the inhalation of the saline aerosol may assist in raising bronchial secretions from the smaller bronchi and bronchioles particularly in those individuals with a weak or ineffective spontaneous cough.

The various alterations in cell morphology and the many bizarre forms of respiratory epithelium observed on cytologic study of sputum from patients with chronic pulmonary disease have recently been reported by Papanicolaou,[16] and Farber and his associates[17] who emphasized the need for rigid criteria in differentiating apparently benign metaplastic changes from carcinoma. From these reports and others, there is some evidence that the bronchial epithelium reaction leading to malignancy may be manifest for some time before the clinical diagnosis of lung cancer is possible.

Cytologic examination of the 74 sputum specimens recovered following the inhalation of 10 per cent saline aerosol indicated that the majority of the specimens expectorated contained respiratory epithelium and alveolar phagocytes. Cellular morphology was well preserved so that the clear cut differentiation between abnormal and normal cells was readily apparent to the experienced pathologist. In addition to the value of this method of obtaining sputum for the cytologic diagnosis of lung malignancy, the importance of bacteriologic as well as cytologic examination of induced sputum deserves further emphasis, especially in those patients with undiagnosed respiratory disease from whom no spontaneous sputum is available for study.*

SUMMARY

A method of obtaining sputum from the respiratory tract of "normal" individuals, patients with chronic non-tuberculous pulmonary disease, and patients with known or suspected malignancy is reported. The basis of this procedure involves the inhalation of warm, hygroscopic saline aerosols.

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*Since this paper was written significant developments in the principles and technics of aerosol deposition have been made. At temperatures of 120° to 130° F., 10 liters of air contain 0.185 gm H_2O, at 120° F., 0.789, at 140° F. 1.302 gm H_2O. Over a period of 30 minutes inhalation approximately 11 cc. of water would theoretically be deposited on the laryngo-tracheo-bronchial mucous membrane at 120° F., and 39 cc. at 140° F. In an aerosol administered at 98° F. the particles are preserved by the humidified atmosphere but significant *enhanced* "rain-out" effect takes place *above* body temperature. The clinical advantages of inhaling aerosols with controlled temperatures of 120° F. and 130° F. in patients with bronchial asthma, pulmonary emphysema, and a variety of respiratory disorders characterized by difficulty in eliminating retained bronchial secretions will be reported later. (Barach, Alvan L., Beck, G. J., and Bickerman, H. A.).

Approximately 10 ml. of a 10 or 15 per cent saline aerosol containing 20 per cent propylene glycol was administered to a total of 336 subjects. Mucoid sputum specimens suitable for cytologic examination were recovered in 88.5 per cent of the entire series. Of special interest as a possible screening technic for the cytologic diagnosis of lung cancer was the production of sputum in 86 per cent of 180 subjects who had no evidence of pulmonary disease, and no cough or spontaneous sputum. Only three subjects in this group noted a slight irritation on inhaling the warm 10 per cent saline aerosol.

Cytologic studies of the sputum recovered from 74 subjects following the inhalation of 10 per cent saline showed that 79 per cent of the specimens were satisfactory for diagnosis. In five of the eight patients with documented primary or metastatic carcinoma in the lung, sputum preparations were positive for malignant cells. There were no false negative reports. Since all of the examinations were performed on single specimens, it is evident that cytologic study of repeated specimens obtained in a similar manner might increase the possibilities of accurate diagnosis. It is the opinion of our cytologist (E. E. S.) that this method of inducing sputum may be expected to demonstrate tumor cells from symptomless individuals before spontaneous sputum arises since the specimens obtained by hypertonic saline aerosol are entirely adequate for study.

Inhalation of nebulized 20 per cent propylene glycol at a temperature of 120° F. is employed to facilitate expectoration of retained secretions in patients with bronchopulmonary disease.

RESUMEN

Se describe un método para obtener esputo de las vías respiratorias de los individuos "normales" con enfermedad crónica no tuberculosa y enfermos sospechosos o averiguados de padecimientos malignos.

La base de este procedimiento radica en la inhalación de aerosoles calientes, de soluciones salinas higroscópicas.

Aproximadamente se usaron 10 ml. al 10 o 15 por ciento de un aerosol conteniendo 20 por ciento de propilen glicol en un total de 336 sujetos. Se obtuvo un espécimen mucoide adecuado para estudio citológico en 88.5 por ciento de los casos.

Es de interés especial este método como uno para la detección del cáncer por la citología ya que se obtuvo esputo en 86 por ciento de personas entre 180 sujetos que no tenían evidencia de enfermedad ni tos ni expectoración. Sólo tres personas de este grupo notaron ligera irritación al inhalar la solución caliente al diez por ciento en aerosol.

Los estudios citológicos en el esputo de 74 personas después de la inhalación de la solución salina al 10 por ciento, mostró que 79 por ciento de los especímenes fueron satisfactorios para el diagnóstico. En cinco de ocho enfermos comprobados de carcinoma primario o metastásico las preparaciones de esputos fueron positivas para células malignas. No hubo informes falsos negativos. Puesto que todos los exámenes se hicieron en sólo una muestra, es evidente los estudios en muestras repetidas hechas

en forma similar han de dar mayor proporción de diagnósticos exactos. El citologista opina (E.E.S.) que este método de provocar el esputo puede esperarse que muestre celdillas tumorales de individuos asintomáticos antes de que obtenga esputo espontáneo ya que los especímenes fueron completamente adecuados para el estudio.

RESUME

L'auteur présente une méthode qui permet d'obtenir des crachats provenant de l'arbre respiratoire chez des individus "normaux," chez des malades atteints d'affections pulmonaires chroniques non tuberculeuses, et chez des malades atteints d'affections malignes, connues ou soupçonnées. La base de ce procédé comprend l'inhalation d'aérosols salins, chauds et hygroscopiques.

Environ 10 cc. d'un aérosol à 10 ou 15% de sel, contenant 20% de glycol propylene, a été administré à un nombre total de 336 malades. Des types d'expectorations mucoïdes propres à l'examen cytologique furent recueillis dans 88,5% de la totalité du groupe. La production d'expectoration dans 86% des cas, sur 180 malades chez lesquels on n'avait pu mettre en évidence une affection pulmonaire, et qui n'avait ni toux ni expectoration spontanée, fut d'un intérêt particulier, pour permettre le diagnostic cytologique de cancer pulmonaire. On observa chez trois sujets seulement de ce groupe une irritation légère lors de l'inhalation de l'aérosol chaud contenant 10% de sel.

Les études cytologiques sur l'expectoration recueillie chez 74 malades après inhalation de solution à 10% de sel, montrèrent que 79% des spécimens d'expectoration furent satisfaisants pour le diagnostic. Chez cinq malades sur 8 qui étaient atteints de cancer pulmonaire métastatique ou primitif prouvé, les expectorations montrèrent l'existence de cellules malignes. Il n'y eut aucun cas d'erreur. Comme tous les examens furent pratiqués sur un simple échantillon, il est évident que l'étude cytologique d'échantillons multiples obtenus dans des conditions semblables pourrait augmenter les possibilités d'un diagnostic précis. Notre cytologiste exprime l'opinion que cette méthode d'obtenir une expectoration pourrait amener à mettre en évidence des cellules tumorales chez des individus sans symptômes, avant qu'une expectoration spontanée ne survienne, étant donné que les échantillons obtenus par aérosol salin hypertonique se prêtent parfaitement à l'étude.

ZUSAMMENFASSUNG

Es wird berichtet über eine Methode zur Gewinnung von Sputum aus dem Respirationstrakt von "normalen" Individuen, Patienten mit chronischen nicht tuberkulösen Lungenkrankheiten und Patienten mit bekannten oder als solche angenommenen bösartigen Veränderungen. Die Grundlage dieses Vorgehens macht die Inhalation von warmen, hygroskopischen Salz-Aerosolen notwendig.

Ungefähr 10 ccm einer 10-oder 15% Salz-Aerosol-Lösung, die 20% Propylen-Glycol enthielt, wurde insgesamt bei 336 Personen angewandt. Für die cytologische Untersuchung geeignete Schleimhaltige Sputumpräparate wurden in 88,5% der ganzen Serie gewonnen. Von speziellen Inter-

esse als eine mögliche Suchtechnik zur cytologischen Diagnose des Lungenkrabses war das Zustandekommen von Auswurf bei 86% von 180 Personen, bei denen kein Anhalt für eine Lungenkrankheit bestand, also auch kein Husten und auch kein spontaner Auswurf. Nur 3 Personen aus dieser Gruppe bemerkten eine leichte Reizung bei der Inhalation der warmen 10%igen Salz-Aerosol-Lösung.

Cytologische Untersuchungen aus dem Sputum, das von 74 Personen nach der Inhalation von 10% Salzlösung gewonnen war, zeigte, dass 79% der Präparate zur Diagnose ausreichend waren. Bei 5 der 8 Patienten mit nachgewiesenem primären oder metastatischen Lungenkrabs waren die Sputumpräparate positiv hinsichtlich Tunorzellen. Es gab keine irrtümlich negativen Befunde. Da alle diese Untersuchungen *mit jeweils einem* einzigen Präparat durchgeführt wurden, ist es augenscheinlich, dass cytologische Studien von mehrfach wiederholtem Untersuchungsmaterial das in ähnlicher Weise gewonnen wurde, die Möglichkeiten einer genauen Diagnose erhöhen könnte. Nach der Meinung unseres Zellspezialisten (E.E.S.) kann man von dieser Methode der Sputumgewinnung erwarten, dass sie Tumorzellen zum Nachweis bringt bei erscheinungsfreien Personen, ehe Spontansputum entsteht, da die Präparate, wie sie mit hypertonischer Salz-Aerosol-Lösung erzielt werden, für die Untersuchung völlig ausreichen.

REFERENCES

1 Gerhardt, P. R., Handy, V. H. and Ferber, B.: "Trends in Cancer Incidence, Mortality and Probability in the State of New York," *N. Y. State J. Med.*, 57:1387, 1957.

2 Kupa, E. and Breslow, L.: "The Crossing of the Curves: Tuberculosis and Lung Cancer," *Dis. Chest*, 31:23, 1957.

3 Lutwyche, V. U.: "Bronchial Carcinoma: A Review of 116 Cases," *Brit. J. Tuberc.*, 50:294, 1956.

4 Davies, D. F.: Personal communication.

5 Hampeln, P.: "Zur symptomatologie und diagnose der primaren malignen lungentumoren," *Mitt a.d. Grensgeb. d. Med. u. Chir.*, 31:672, 1918.

6 Wandall, H. H.: "A Study of Neoplastic Cells in Sputum as a Contribution to the Diagnosis of Primary Lung Cancer," *Acta Chir. Scandinav.*, 91: Supp. 93, 1944.

7 Umiker, W.: "The Typing of Bronchogenic Carcinoma by Cytologic Smear Examination," *Univ. Mich. Med. Bull.*, 22:287, 1956.

8 Hampson, F.: "Exfoliative Cytology in the Diagnosis of Lung Cancer: Examination of One Laboratory's Results," *Brit. M. J.*, 2:1461, 1956.

9 Papanicolaou, G. N. and Trout, H. F.: *Diagnosis of Uterine Cancer by the Vaginal Smear.* Commonwealth Fund, New York, 1943.

10 Farber, S. M., McGrath, A. K., Benioff, M. A. and Espen, L. W.: "The Early Diagnosis of Primary Lung Cancer by Cytologic Methods," *Dis. Chest*, 20:237, 1951.

11 Findeisen, W.: "Uber des absetzen kleiner in der luft suspendierte teilchen in der menschlichen lunge bei der atmung." *Arch. f.d. ges. Physiol.*, 236:367, 1935.

12 Wilson, I. B. and La Mer, V. K.: "The Retention of Aerosol Particles in the Human Respiratory Tract as a Function of Particle Radius," *J. Indust. Hyg.*, 30:265, 1948.

13 Abramson, H. A.: *Aerosol Therapy in Medical Physics.* P. 823, Vol. II. The Year Book Publishers, Inc. Chicago, Ill., 1950.

14 Talbot, T. R., Jr., Quimby, E. H. and Barach, A. L.: "A Method of Determining the Site of Retention of Aerosols within the Respiratory Tract of Man by the Use of Radioactive Sodium," *Am. J. Med. Sc.*, 213:585, 1947.

15 Barach, A. L., Garthwaite, B. and Bickerman, H. A.: "Therapeutic Uses of Penicillin Aerosol," *Postgrad. Med.*, 5:4, 1949.

16 Barach, A. L., Mason, W. and Jones, B. P.: "The Effect of the Administration of Hypertonic Salt Solution on the Blood Volume and Certain Related Blood Constituents," *Arch. Int. Med.*, 30:668, 1922.

17 Papanicolaou, G. N.: "Degenerative Changes in Ciliated Cells Exfoliating from the Bronchial Epithelium as a Cytologic Criterion in the Diagnosis of Diseases of the Lung," *N. Y. State J. Med.*, 56:2647, 1956.

18 Farber S. M., Wood, D. A., Pharr, S. L. and Pierson. B.: "Significant Cytologic Findings in Non-Malignant Pulmonary Disease," *Dis. Chest*, 31:1, 1957.

Chronic Pneumonitis Simulating Bronchiogenic Carcinoma

EARL B. SANBORN, M.D., F.C.C.P.*
Evanston, Illinois

Although there has been an improvement in the mortality, morbidity, and five year survival rates for those undergoing operative procedures for cancer of the lung, there are many afflicted with the disease who reach the thoracic surgeon too late for satisfactory surgical therapy, the only accepted curative method available today. All members of the medical profession concerned with this problem realize that a more aggressive approach is necessary in certain clinical conditions.[1-2] "Recurrent" or "unresolved" pneumonias fall in this latter group. The inflammatory reaction may result from intermittent or persistent obstruction of bronchial secretions due to neoplasm or its associated pathology.

Experience with several patients, who were suspected of having bronchiogenic carcinoma, demonstrated the need for conservatism in such cases.

Case 1: A. B., a 66 year old Negro, was admitted to the hospital with a small, firm, slightly movable mass at the vertex of the scalp. This had increased in size during the preceding eight months until it measured 2 x 1.5 cm. Physical examination was otherwise not significant. Hematological determinations were normal except for the sedimentation rate of 34 mm. Smears of three sputum specimens were negative for tuberculi bacilli. The blood serology was positive, but that of the spinal fluid was negative. Roentgenograms of the thorax, postero-anterior (Fig. 1) and right lateral views, revealed a density extending from the hilum into the right lung field with overlying pleural reaction anteriorly.

History of cough, of right anterior chest pain for 18 months, and twelve pound weight loss was elicited. Bronchoscopy revealed no abnormality. Aspirated bronchial secretions utilizing paraffin sections (of cell blocks) were negative for tumor cells. The scalp lesion was excised and reported as an epidermal inclusion cyst. Several loose teeth were removed. The usual pre-operative routine was completed except that 300,000 units of penicillin were given twice daily for 12 days because of the positive blood serology. At operation adhesions were found extending from a firm mass in the upper and middle lobes of the right lung to the anterior chest wall and to the mediastinum. Pneumonectomy was performed.

The specimen consisted of the right lung weighing 500 grams. The segmental bronchi of the middle lobe and anterior segment of the upper lobe were stenosed and surrounded by a firm mass, 8 x 6.5 x 6 cm. The fairly dry lesion consisted mostly of grayish-green tissue which extended antero-laterally. At only one point was the overlying pleura dimpled and attached. The remainder of the lung parenchyma was not remarkable except for congestion due to surgery and apical subpleural emphysematous blebs. Microscopic examination revealed many macrophages with oval, eccentrically placed nuclei and many small vacuoles (stained with Scarlet Red) in the cytoplasm. These cells were seen in the areas of acute and chronic inflammation. The pathologist reported chronic pneumonitis, cholesterol type.

His condition during and following operation was satisfactory. During a period of 17 months he had three follow-up visits. Roentgenograms

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*Associate in Surgery, Chicago Medical School.

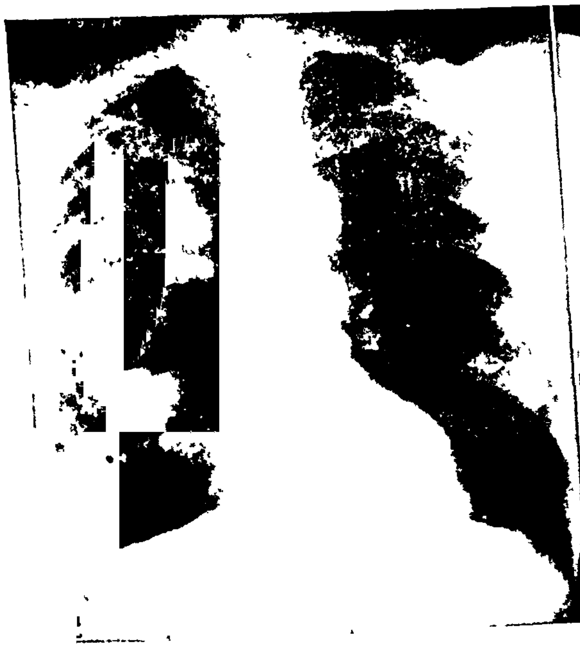

FIGURE 1

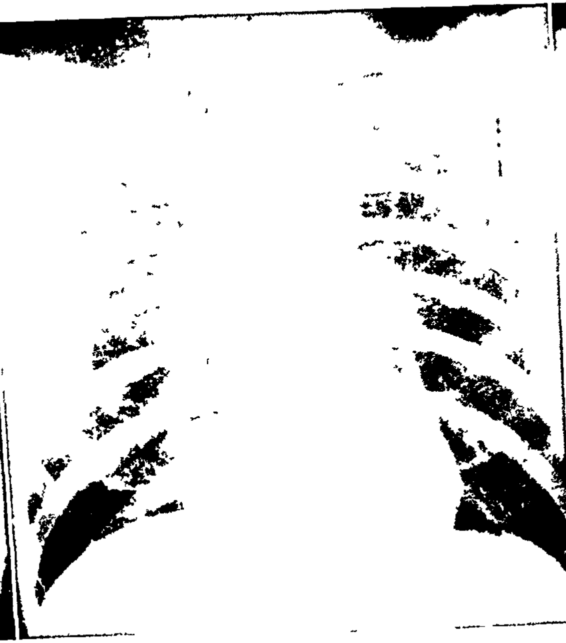

FIGURE 2

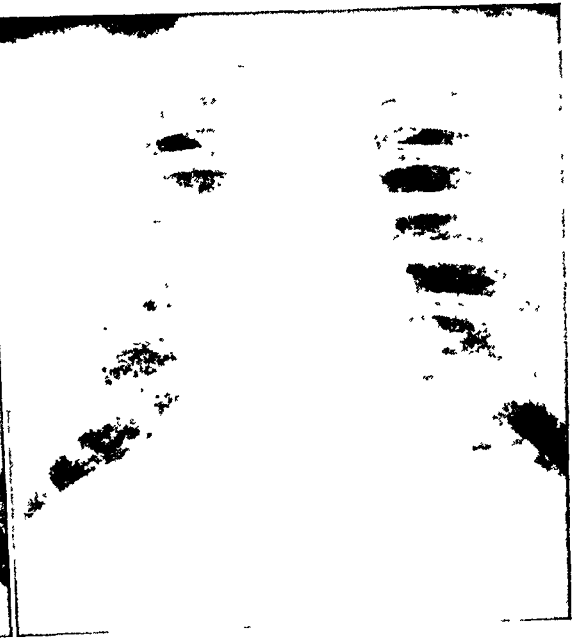

FIGURE 3

Figure 1 (Case 1): Roentgenogram showing hilar mass extending into the right lung field suspicious of bronchiogenic carcinoma.—*Figure 2* (Case 2): Roentgenogram showing right hilar mass characteristic of carcinoma of the lung.—*Figure 3* (Case 3): Roentgenogram showing mass in right upper lobe suspicious of bronchiogenic carcinoma.

revealed the mediastinal structures markedly deviated to the right with some herniation of the well aerated, normal left lung through the mediastinum. The right hemithorax was opaque. Vital capacity was 45.7 per cent of normal, and maximum breathing capacity was 31 per cent of normal. The immediate post-operative dyspnea diminished. He had gained nine pounds in weight and was able to work as a janitor when last seen.

Case 2: J. J. W., a 41 year old Negro, landscape gardener, was transferred from another hospital with a cough productive of clear mucoid sputum for one year. Within the past three months two teeth had been extracted. Because of weakness he had discontinued work. Two episodes of hemoptyses, each of which included more than a cupful of blood, and was precipitated by coughing, occurred respectively one week and two days before admission. Dyspnea was noted after the first episode. After the second hemoptysis a roentgenogram was taken and he was told of a "growth" in the right lung. Additional questioning disclosed some right chest pain and occasional expectoration of foul-smelling sputum.

Physical examination revealed several missing teeth and others in poor condition, limitation of motion of the right hemithorax, and dullness posteriorly in the right mid-thoracic area with breath sounds diminished over the same area. His hemoglobin was 11.5 grams. Tubercle bacilli were not found in smears of two sputum specimens. A roentgenogram (Fig. 2) revealed a density in the right hilar region which extended laterally and anteriorly to the pleural surface.

Bronchoscopy was performed without significant pathological findings. Bronchial secretions were negative for tumor cells. Thoracotomy revealed a firm palpable mass in the anterior contiguous portions of the upper and middle lobes of the right lung. Bilobectomy was done. Frozen section of the specimen revealed no neoplastic tissue.

The specimen consisted of the upper and middle lobes of the right lung weighing 236 grams. The pleura was smooth except for an area of scarring over the latero-posterior surface. In this area lying on both sides of the fissure, approximately 4 cm. from the periphery of the lung, was a firm rounded, fairly discrete grayish mass measuring 6 x 4.5 x 2.5 cm. Its center contained an area of cavitation (1.5 cm. in diameter) which had an ill defined wall covered by a shaggy exudate. The remainder of the specimen was crepitant to palpation. Lymph nodes about the upper and middle lobe bronchi were small, soft and anthracotic.

Microscopical sections of the mass showed interstitial chronic reaction and fibrosis. The overlying pleura was thickened by numerous dilated vessels and loose edematous fibrous tissue. Cells with clear or foamy refracticle cytoplasm were present in many scattered areas. An abscess with cavitation was in the center of the lesion surrounded by large areas of organizing pneumonia. The alveoli, in a few focal areas, contained refractile vacuoles and macrophages with numerous small vacuoles giving them a foamy appearing cytoplasm. On proper staining the macrophages were seen to contain fat. Sections of lymph nodes revealed hyperplasia, hyperemia, mild anthracosis, and edema. The pathologist diagnosed chronic pneumonitis with a cavitating abscess of the right upper and middle lobes.

During and following surgery his course was uneventful and he was discharged on the 12th postoperative day.

Two months after discharge he reported seven pounds gain in weight. Physical and roentgenological examinations disclosed no abnormality of the remaining lung. Four days later he had evidence of jaundice. He was readmitted to the hospital and gave a history of two previous episodes of "yellow jaundice." After clinical and laboratory studies resulted in the diagnosis of acute hepatitis due to homologous serum jaundice, treatment was initiated with satisfactory results.

Seven months after operation his vital capacity was 3,000 cc. (60 per cent of normal). Laboratory examinations revealed no evidence of hepatitis. One year after operation he had gained 50 pounds and was attending school.

Case 3: L. R., a 54 year old laborer, was transferred from another hospital with the diagnosis of pneumonitis and bronchiogenic carcinoma of the right lung. Two months previously he had noted the onset of lassitude and inability to work two consecutive days because of fatigue. One month later dyspnea and anorexia were noted as well as knife-like right upper chest pain aggravated by coughing. In addition he had lost 10 pounds in weight. Cough productive of yellow, tenacious sputum developed. He was admitted to the other hospital because of fever. Aureomycin was discontinued after eight days because of marked improvement. A relapse occurred five days later and aureomycin was initiated again for eight more days. At intervals roentgenograms of the chest strongly suggested bronchiogenic carcinoma. Bronchoscopy was performed, and the aspirated secretions were interpreted as compatible with primary carcinoma, undifferentiated type.

Physical examination revealed alopecia of the left parieto-occipital region, carious teeth and pyorrhea, diminished breath sounds and occasional fine rales over the right upper anterior thorax, and exostosis of the right first metatarso-phalangeal joint. His pulse rate was 100 and blood pressure 170/100.

Hematological, serological, and chemical examinations were unrevealing. Several sputum examinations were negative for tubercle bacilli. Roentgenograms (Fig. 3) showed a hazy indistinct infiltration of the anterior portion of the upper lobe to the right. Comparison with roentgenograms previously made revealed that originally a much larger area of infiltration had been present. The radiologist interpreted the findings as consistent with the diagnosis of bronchiogenic carcinoma.

After a review of the clinical and laboratory data the parenchymal process was considered inflammatory. However, considering his age, and the relatively large amount of residual inflammation, exploratory thoracotomy was considered obligatory. Bronchoscopy and bronchial secretions showed no evidence of neoplasm.

At thoracotomy a firm mass in the anterior portion of the upper lobe of the right lung was found adherent to the chest wall and mediastinum by firm thick vascular adhesions. A firm lymph node located inferior to the axygos vein, and several small pieces of the mass were removed, which were negative for neoplasm. *Only the anterior segment* of the right upper lobe was removed. The pathologist reported that this specimen showed chronic fibrosing pneumonitis.

The segmental bronchus appeared entirely normal. The peribronchial tissue was moderately firm and upon section appeared to be replaced by dull gray fibrous tissue. In no area was there evidence of neoplasm, cyst, or abscess. The accompanying lymph node appeared normal in size and consistency on viewing its surface. Microscopic examination revealed a large ganulomatous area consisting of interlacing bands of fibrous tissue containing a few scattered lymphocytes and an occasional polymorphonuclear leukocyte. There were giant cells in which 3 or 4 nuclei were arranged centrally or peripherally. No areas of necrosis were seen. The overlying pleura was greatly thickened by dense hyalinized fibrous tissue in which there were a few small vessels. In some sections there were discrete areas in which the pulmonary parenchyma was entirely replaced by fibrous tissue. In these areas there were numerous lipophages and foci of acute and chronic inflammation. No evidence of malignancy was seen. Examination of the lymph node from the region of the right main stem bronchus revealed a mild lymphoid hyperplasia and a moderate amount of anthracotic pigment. The pathologist reported chronic pneumonitis, etiology undetermined, in the segment of lung removed.

The postoperative course was uneventful and he was discharged.

One month later he was readmitted for excision of the exostosis of the first metatarso-phalangeal joint. Roentgenograms revealed no evidence of disease then or one year later when he reported that he was well.

Discussion

How *aggressive* should the medical profession be in the management of patients who roentgenograms reveal evidence of persisting pulmonary lesions suggesting bronchiogenic carcinoma? Clinicians who reviewed the preoperative clinical, roentgenological, and laboratory findings in these three cases did not hesitate to recommend surgery inasmuch as they could not be certain that carcinoma did not exist. Bronchoscopy, cardiorenal tests, and the patient's general condition did not contraindicate thoracotomy in any of them. In the operating room gross appearance and palpation were found to be insufficient criteria for definitive diagnoses. The Pathology Department assumed responsibility for the histological diagnosis by doing frozen sections at the time of operation in the last two cases. Thus, the aggressive attitude of clinicians combined with the judgment of surgeons and pathologist results in better care of the patients. Undoubtedly an aggressive policy indicates that more clinicians who see patients with persistent signs and symptoms of pneumonitis should request serial roentgenograms. If this is done, more pulmonary pathology, including early cases of carcinoma of the lung will be recognized.

How long should one observe or treat medically a patient with pneumonitis (viral or atypical, unresolved or recurrent)? Experience with two other patients each of whom had a small bronchiogenic carcinoma obstructing a segmental bronchus demonstrated that one should not observe patients for long periods without taking action. The first patient, a 56 year old negro, had a cough and anorexia for one month preceded by some weakness and loss of weight. Although bronchoscopy was negative, serial roentgenograms, during one month of observation, demonstrated recurrence of segmental atelectasis and pneumonitis of the right upper lobe. The second patient, a 75 year old man, had had initial symptoms of chills and fever three months previously and was treated elsewhere for pneumonia. Subsequently he had developed weakness and loss of weight and was admitted to another hospital. It should be noted that he always had chronic cough; however, it became more productive and was intermittently sanguinous after the onset of the above symptoms. During the evaluation of complaints referable to the genitourinary and gastrointestinal systems he had another episode of pneumonitis. This was demonstrated by increase in the disease of the upper lobe of the left lung as seen on roentgenograms. Each of these patients had upper lobectomy.

Since patients should be evaluated individually, one cannot safely propose general rules for all. One may conclude, however, that it is unwise to postpone exploratory thoracotomy more than eight weeks in a 35-40 year or older person who has unresolved or recurrent pneumonia, or lobar or segmental atelectasis, unless there is a contraindication. This type of management is especially advised if the patient is a man, has been a heavy smoker, or has significant symptoms.

Frequently the attending physician will prolong the diagnostic and observation period in cases of "pneumonitis," which have thoracic roentgenograms suggestive of carcinoma of the lung, and thus delay operative intervention too long. The results of laboratory tests made over a long period of time may be misleading and also indecisive. A negative result of the study of sputum, or bronchial secretions, does not necessarily rule out a malignant pulmonary lesion. Likewise a positive test may be erroneous (Case 3). Cases are known in which total pneumonectomy was done because of a positive Papanicolaou test of bronchial secretions or sputum; in two cases the pathologists found no evidence of a malignant lesion in the surgical specimen.

How far should a *conservative* policy be carried by the surgeon? After experience with Case 1 it was decided to have a histological diagnosis (of the pathological pulmonary tissue) before any significant resection was done. As a result more limited excisions were performed in Cases 2 and 3. This proved wise for no neoplastic process was present in the surgical specimens. Larger resections would have unnecessarily removed some functioning pulmonary tissue and would have been too radical. Conservative management, especially in the third patient, where a diagnosis of bronchiogenic carcinoma had been made elsewhere, was of value to the patient.

A number of authors have contributed to the development of the policy of *aggressive conservatism.* Paulson and Shaw[1] emphasized the significance of pneumonitis in a study of 362 patients with bronchiogenic carcinoma. They found viral or atypical pneumonias and unresolved pneumonia to be two of the commonest erroneous diagnoses which contributed to the delay in treatment. Ochsner *et al*[2] reported that a lower respiratory tract infection was frequently the earliest manifestation of a bronchiogenic carcinoma. In their series of 948 patients, 55 per cent gave histories of previous respiratory tract infection diagnosed either as influenza, viral pneumonia, or non-specific pneumonitis. Such an infection was the first manifestation in 22 per cent of their patients. After their recovery from pneumonitis there were persistent symptoms! Freedlander and Wolpaw[3] and Adams,[4] urged resection of inflammatory lesions of the lung because of the difficulty in differentiation from carcinoma. In a classic article, Waddell, Sniffen and Sweet[5] reported that six of 10 cases of chronic pneumonitis had a preoperative diagnosis of carcinoma of the lung. There is, then, much evidence that good judgment is needed in the management of such cases.

SUMMARY AND CONCLUSIONS

In cases of viral, or atypical, and unresolved or recurrent pneumonias, with persistent roentgenological findings suggestive of carcinoma of the lung, the attending physician should consider consulting a well trained thoracic surgeon concerning the advisability of thoracotomy for diagnostic and therapeutic purposes.

The surgeon responsible for such a patient cannot depend entirely on the results of laboratory studies of bronchial secretions and sputum. At the time of operation his decision concerning the amount of pulmonary tissue to be resected should be based on a pathological examination of an adequate biopsy of the diseased tissue.

Experience with three patients with suspicious thoracic roentgenological findings illustrates the advisability of a policy of *aggressive conservatism.*

RESUMEN Y CONCLUSIONES

En casos de neumonías, de virus, o atípicas y neumonías no resueltas o recurrentes con hallazgos radiológicos sugestivos de carcinoma del pulmón, el medio tratante debe considerar la necesidad de consultar con un cirujano de tórax bien preparado respecto de la toracotomía con fines diagnósticos y terapéuticos.

El cirujano responsable de tales enfermos no puede fiarse enteramente de los estudios de laboratorio de las secreciones bronquiales y del esputo. Durante la operación su decisión respecto de la cantidad de pulmón que ha de resecarse debe basarse en el examen histopatológico con biopsia adecuada.

La experiencia en tres enfermos con hallazgos roentgenológicos sospechosos a los rayos X ilustra lo aconsejable que es una actitud *conservadora agresiva.*

RESUME

En présence de pneumopathies à virus, ou de pneumonies atypiques, et des formes résistantes au traitement ou donnant lieu à une rechute, avec constatations radiologiques persistantes, évocatrices de carcinome pulmonaire, le médecin traitant devrait envisager de consulter un chirurgien thoracique bien expérimenté sur la nécessité de pratiquer une thoracotomie dans un but diagnostique et thérapeutique.

Le chirurgien responsable d'un tel malade ne peut pas se fier entièrement aux résultats des études de laboratoire des sécrétions bronchiques et des expectorations. Au moment de l'opération, sa décision concernant la quantité de tissu pulmonaire qui doit être réséquée devrait être basée sur l'examen anatomo-pathologique d'une biopsie bien exécutée du tissu atteint.

L'auteur rapporte le cas de trois malades pour lesquels les constatations radiologiques thoraciques étaient suspectes et qui illustrent l'opportunité d'un programme de "conservatisme agressif."

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

In Fällen Viruspneumonien oder atypischen und ungeklärten oder rezidivierenden Pneumonien mit auf Lungencarcinom verdächtigen beständigen röntgenologischen Befunden muss der behandelnde Arzt in Erwägung ziehen, einen gut erfahrenen Thorax-Chirurgen zu konsultieren hinsichtlich der Zweckmässigkeit einer Thorakotomie aus diagnostischen und therapeutischen Gründen.

Der für einen solchen Kranken verantwortliche Chirurg kann nicht ganz abhängig sein von den Ergebnissen von Laboratoriums-Untersuchungen von Bronchialsekreten und Sputum. Zum Zeitpunkt der Operation muss sich seine Entscheidung hinsichtlich des Ausmasses von zu resezierendem Lungengewebe stützen auf eine pathologisch-anatomische Untersuchung einer adaequaten Biopsie des erkrankten Gewebes. Erfahrung mit 3 Patienten mit verdächtigen Thorax-Röntgenbefunden erläutert die Zweckmässigkeit einer Methode des *agressiven Konservativismus.*

REFERENCES

1 Paulson, D. L. and Shaw, R. R.: "Early Detection of Bronchiogenic Carcinoma," *J.A.M.A.*, 146:525, 1951.

2 Ochsner, A., DeCamp, P. T., DeBakey, M. E. and Ray, C. J.: "Bronchiogenic Carcinoma, Its Frequency, Diagnosis, and Early Treatment," *J.A.M.A.*, 148:691, 1952.

3 Freedlander, S. O. and Wolpaw, S. E.: "Chronic Inflammatory Lesions of the Lung Simulating Bronchiogenic Carcinoma," *J. Thor. Surg.*, 9:530, 1940.

4 Adams, W. E.: "Chronic Nonspecific Suppurative Pneumonitis," *Surgery*, 22:723, 1947.

5 Waddell, W. R., Sniffen, R. C. and Sweet, R. H.: "Chronic Pneumonitis: Its Clinical and Pathological Importance," *J. Thor. Surg.*, 18:707, 1949.

Cycloserine-Isoniazid Combination Therapy in Virgin Cases of Pulmonary Tuberculosis

ISRAEL G. EPSTEIN, M.D., F.C.C.P., K. G. S. NAIR, M.D., LINN J. BOYD, M.D.
and PAUL AUSPITZ, M.D., F.C.C.P.**
New York, New York

Cycloserine* (CS) is an antibiotic produced by *Streptomyces orchidaceous*.[1] It is of low molecular weight, and is readily soluble in body fluids. The determination of CS in body fluids has been facilitated by the chemical method devised by Jones.[2] Cycloserine has been shown to penetrate readily into the body cavities, and to be excreted in the sputum, saliva, urine, bile, and mother's milk. It also enters the spinal fluid and the fetal blood by way of the placenta.[3, 4] Although CS is a broad-spectrum antibiotic,[5-8] its primary usefulness has been established in the treatment of tuberculosis.[9] It is excreted into the urine in high concentrations,[5] and has been found useful in the treatment of urinary infections.[8]

Against the tubercle bacillus, CS is effective *in vitro* in higher concentrations than those obtained with isoniazid (INH) or streptomycin.[5, 10] However, its easy absorption into the blood stream[5] and virtually universal distribution into the tissues[3] results in higher plasma and tissue concentrations than is the case with other antituberculosis agents. For this reason, although CS is less effective than INH *in vitro*, the clinical dose is approximately the same, i.e., 5 to 10 mg./Kg. of body weight per day.

Cycloserine has been shown to be effective in previously untreated cases of tuberculosis, but has proved especially useful in chronic, resistant cases.[9, 11-14] In addition, it will be shown in this presentation that sensitivity of the tubercle bacillus during treatment with CS falls rather slowly, and seldom reaches serum concentrations that cannot be attained clinically.[15] True resistance to CS develops but rarely, if at all.

Cycloserine-Isoniazid Combination Therapy in Tuberculosis

The upper limits of CS dosage are set by the neuropsychiatric symptoms which sometimes develop during continued administration. These will be discussed in detail and related to plasma concentrations of CS in another report. Some data on CS-INH combination therapy have been presented in preliminary and interim reports.[15, 16] Details of the

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**From the Departments of Medicine and Pulmonary Diseases, New York Medical College, Metropolitan Medical Center.

*Manufactured by Commercial Solvents Corporation, Terre Haute, Indiana, and marketed by Eli Lilly and Company, Indianapolis, Indiana as 'Seromycin' (Cycloserine, Lilly).

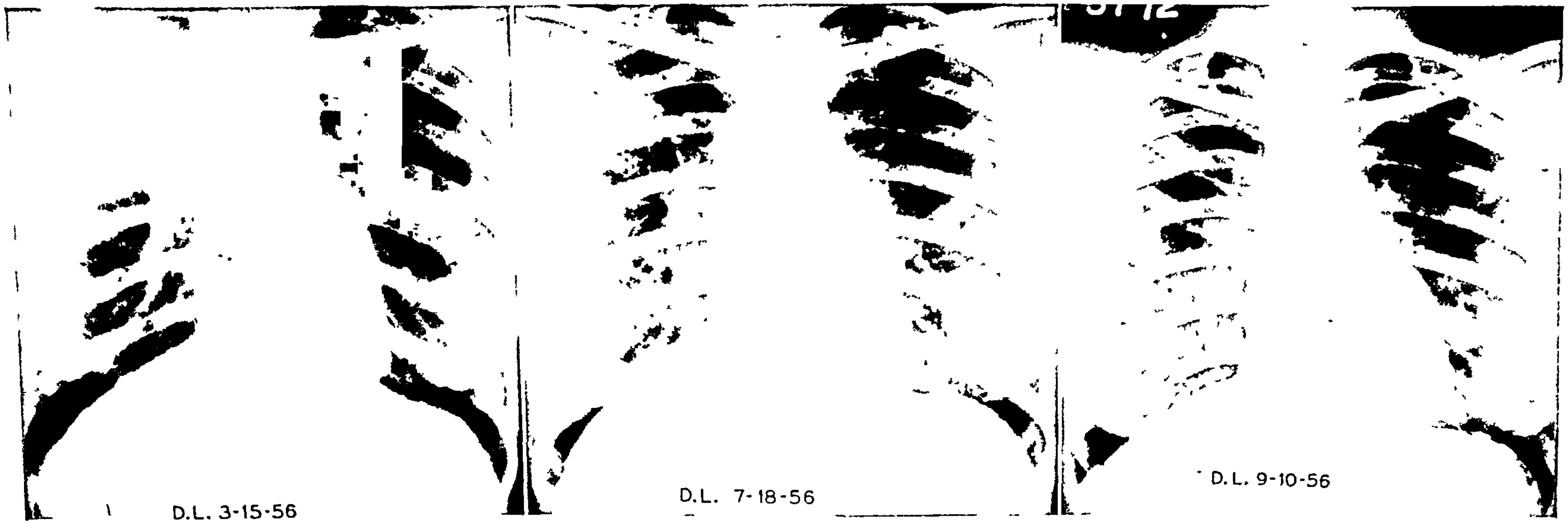

FIGURE 1A FIGURE 1B FIGURE 1C

FIGURE 1: Patient D. L., a 22 year old Puerto Rican woman, was admitted with a two weeks' history of loss of weight, anorexia, night sweats, and cough. Admission sputum showed tubercle bacilli on smear, and x-ray film of the lungs revealed a caseous pneumonic lesion of the right upper lobe (Fig. 1A). She was started on cycloserine, 0.25 Gm. and isoniazid, 0.15 Gm. twice daily. There was prompt and marked symptomatic improvement. After six weeks of therapy, the sputum and gastric contents were devoid of tubercle bacilli on smear and culture. Serial x-ray films showed slight improvement on the sixth week, moderate improvement on the 17th (Fig. 1B) and 24th weeks, and marked improvement on the 26th week (Fig. 1C) of therapy. She gained 52 lb. in weight during her hospital stay. After six months of hospitalization, she was discharged to the Out-patient Clinic and continued on the combination therapy.—*Figure 1A:* X-ray film of the lungs taken on admission shows a caseous pneumonic lesion in the right upper lobe.—*Figure 1:* X-ray film taken after 17 weeks of therapy shows moderate improvement of the right upper lobe lesion.—*Figure 1C:* X-ray film taken after 26 weeks of therapy shows almost complete clearing of the right upper lobe.

clinical procedure used during this study will therefore not be presented here.

No randomization was attempted, but all subjects entering our service at the Metropolitan Hospital were treated with a combination of CS, 0.5 Gm./day, and INH, 0.3 Gm./day, divided in two doses and given morning and evening. In addition to the usual routine observations, an x-ray film of the chest was made monthly, bacterial examination of the sputum was made bimonthly by smear and culture, and when negative, of the gastric contents. Cycloserine plasma levels were obtained at regular intervals, and as dictated by the clinical progress and the appearance of side reactions. Liver and kidney function tests and peripheral blood studies were also done several times during the study.

When tubercle bacilli were isolated from the sputum or gastric contents, they were subjected to routine sensitivity determinations to CS and INH, according to the standards recommended by the VA.[18] These data have been referred to elsewhere,[15] and will be presented in detail in a later report.

Results

As of February 1, 1957, there were 81 patients on the CS-INH combination for from six weeks to 16 months. The dose was CS, 0.25 Gm. and INH, 0.15 Gm., given orally, twice daily. The pretreatment data on these patients are shown in Tables I and II. The severity and acuteness of the tuberculous process is attested to by the fact that 84 per cent of the patients had some degree of fever. Very few early cases are admitted to this hospital, and that is the reason for the low number with minimal x-ray film evidence of disease. All sputa were positive for tubercle bacilli on smear, and confirmed by culture. Presumably, none of the subjects had been treated with antimicrobial agents prior to admission.

Table II shows the x-ray film estimate of pulmonary involvement before the onset of therapy, using the criteria recommended by the National Tuberculosis Association. X-ray film evidence of progress during treatment is shown in Table III. About 40 per cent of the x-ray films showed evidence of improvement within six weeks of treatment. The figure rose to 74 per cent of 74 subjects treated for 12 weeks, and, within six months, to 93 per cent of the 48 remaining subjects.

TABLE I

CYCLOSERINE COMBINATION THERAPY
PULMONARY TUBERCULOSIS
Cycloserine 0.5 Gm. plus INH 0.3 Gm./day, orally

81 Cases			Age: 17-73 Years (Av. 38)
Sex:	Male 55	Female 26	
Race:	White 23	Negro 30	Puerto Rican 24
			Others 4

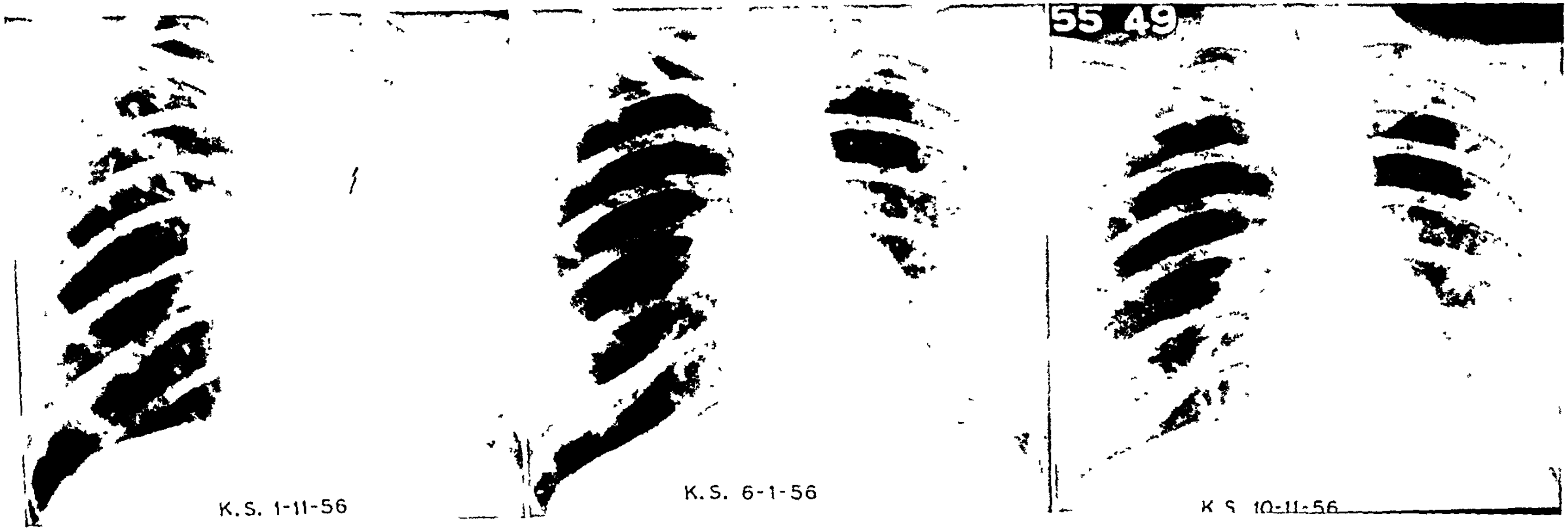

FIGURE 2A FIGURE 2B FIGURE 2C

FIGURE 2: Patient K. S., a 35 year old white woman, was admitted with a two months' history of productive cough, weight loss, anorexia, and night sweats. Admission sputum showed tubercle bacilli on smear, and an x-ray film revealed fibrocavitary tuberculosis involving the entire left lung, with a large cavity in the left upper lobe (Fig. 2A). She was started on cycloserine, 0.25 Gm. and isoniazid, 0.15 Gm. twice daily. After 12 weeks of therapy, the sputum and gastric contents were devoid of tubercle bacilli on smear and culture. Serial x-ray films revealed minimal improvement by the sixth week, *moderate* improvement by the 18th week (Fig. 2B), and marked improvement by the 36th week (Fig. 2C) of therapy. The patient showed symptomatic improvement and gained 34 lb. during her seven months' stay in the hospital. She was then discharged to the Outpatient Clinic and continued on the combination therapy.—*Figure 2A*: X-ray film taken on admission shows an extensive fibrocavitary tuberculosis involving the entire left lung with a large cavity in the left upper lobe, and minimal involvement of the right lobe.—*Figure 2B*: X-ray film taken after 18 weeks of therapy shows moderate improvement of the extensive pneumonic disease in the left upper lobe, and clearing of the right lung.—*Figure 2C*: X-ray film taken after 36 weeks of therapy shows marked reduction of the tuberculous process in both lungs. There is no evidence of the cavity which was present on admission.

There was prompt reduction in the bacillary content of the sputum, as shown in Table IV. At the same time, cough diminished and the amount of sputum lessened and became less purulent. Only those sputa and gastric contents are reported as negative which showed absence of tubercle bacilli on both smear and culture. Within three months, 80 per cent of 64 sputa were bacteriologically negative, and at six months the figure rose to 87 per cent of the sputa. That CS may be presumed to have played a major role in the attainment of these results, is shown by our own data on the treatment of chronic, resistant tuberculosis with CS, 0.5 Gm./day,[13] as well as by the results of others.

Moyer, *et al.*[19] obtained similar data on the sputa of original treatment cases receiving CS alone, 0.5 Gm./day. Within two months of treatment, nine of 12, and at three months, nine of 11 subjects showed sputa negative for tubercle bacilli. Cummings,[20] on data pooled from 10 Veterans Administration Hospitals, reported 35 per cent negative cultures at two months, 61 per cent at four months, and 74 per cent at six months of treatment of original cases of tuberculosis with CS alone, 1.0 Gm./day. Therefore, we feel justified in assigning an important role to the part played by CS in our series of CS-INH combination therapy. and Moyer, *et al.*[19] concluded that, "Cycloserine appears to be of value in the treatment of tuberculosis even at a reduced dosage of a 0.5 gram daily." Isoniazid alone could not account for our results, according to our own unpublished experience. In addition, Russell, *et al.*[21] using INH alone in daily doses of 3.0 to 5.0 mg./Kg. on 286 patients, reported that, ". . . only 37 per cent were bacteriologically negative at four months of therapy; 45 per cent were excreting INH-resistant tubercle bacilli."

Sensitivity tests *showed a slight* decrease of bacillary sensitivity when the dose of CS was 1.0 Gm. or more per day. However, from 0.5 Gm./day of CS *there was no evidence of decreased sensitivity.* Our data, which will be detailed elsewhere, show that "resistance" to CS *did not develop,* and *that the slow* and *slight drop in sensitivity from* the larger doses of CS was not sufficient to interfere with prolonged therapy. Moyer, *et al*[19] reported data similar to ours, in that only one out of 40 subjects produced bacilli which became insensitive to 40 mcg./ml. of CS. From the use of only 0.5 Gm./day of CS, these authors obtained blood levels of CS which were ". . . between 10 and 30

TABLE II

CYCLOSERINE COMBINATION THERAPY
PULMONARY TUBERCULOSIS

Stage of Disease:	Far Advanced	28
	Moderately Advanced	51
	Minimal	2
X-ray Appearance:	Caseopneumonic	24
	Fibrocavitary	57
No. of Patients with Temperature at Start of Therapy: Range: 105° to 99° F.—Average: 100.8° F.		68

mcg./cc., the majority being between 20 and 30 mcg./cc." and their data agree with those of Cummings,[20] and with our own. It is therefore difficult to see how one can ascribe clinical "resistance" to patients with plasma levels of CS of between 20 and 30 mcg./cc. when the tubercle bacilli are inhibited by similar levels of CS *in vitro.*[19] However, we feel that the data are not in accord with the conclusion of Moyer, *et al.*[19] that, "Bacterial resistance to cycloserine occurs rapidly and at about the same degree as that observed when streptomycin or INH is used alone."

Most of the cases treated for more than one month showed rapid development of resistance to INH. These data are not complete, but agree with those of Schwartz and Moyer[22] on the use of INH alone. It appears that CS does not delay the emergence of resistance to INH when the two drugs are administered simultaneously.

Toxic symptoms occur but rarely from 0.5 Gm. of CS per day, alone or in combination with INH.[16, 24-28] From doses of 1.0 Gm. or more per day, the toxicity observed is referable to the central nervous system. These data will be presented elsewhere, and correlated with plasma levels and background conditions, such as inanition, alcoholism, epilepsy, etc. Progress in the study of the origin of these symptoms has been handicapped by the so-called "cycloserine paradox"[29] which extends both to the tuberculous process and to the toxicity, i.e., animals are not readily susceptible to either the antituberculosis or toxic effects of CS[17, 23, 32] as manifested clincally in patients.

Discussion

After establishing proof that CS alone was efficaceous in the treatment of tuberculous subjects, there remained a number of areas for further investigation. One of these is the subject of this report, namely, the effects of therapy with a combination of CS and INH or streptomycin. The results of a preliminary study[16, 25] indicated an additive and possibly synergistic effect between CS and INH, while the results from the CS and strepto-

TABLE III

CYCLOSERINE COMBINATION THERAPY
PULMONARY TUBERCULOSIS
X-Ray Status

	Period (months)				
Degree of Change	1½	3	6	9	12
Marked Improvement	1	12	20	12	6
Moderate Improvement	32	43	25	7	2
Slight to No Change	46	17	3	0	0
Worse	2	2	0	2	0
TOTAL	81	74	48	21	8

mycin combination were inferior. The relatively small number of cases makes it difficult to compare the effects of CS-INH with the usual INH-PAS combinations. However, the clinical results so far obtained by us, and confirmed by Robitzek and Nenashev[14] are consistent with the fact that the CS-INH regimen represents the combination of two potent antituberculous agents, rather than the mere enhancement of the action of INH, as is true for PAS. Toxicity has posed no problem when 0.5 Gm. of CS is used alone or combined with INH, despite the administration of two drugs with somewhat similar neurotoxic effects. Prescott, *et al.*[30] have demonstrated an increased tolerance to INH in mice by the use of CS.

Our impression of synergistic action between CS and INH is supported by the findings of Cummings, *et al.*[10] *in vitro,* and by the results of Schmidt[31] on monkeys, and of Wolinsky and Steenken[17] on guinea pigs. The latter showed that non-antituberculous doses of CS enhanced the therapeutic effects of INH.

SUMMARY AND CONCLUSIONS

1. New, previously untreated cases of pulmonary tuberculosis were treated with a cycloserine-isoniazid combination given orally.

2. Eighty-one cases have been treated for from six weeks to 16 months, with but a single reaction, which did not necessitate discontinuance of treatment.

3. Clinical improvement, reduction of fever, lessening of the volume of sputum, and gain in weight occurred promptly in every case. In addition, the administration of a single capsule containing cycloserine and isoniazid, twice daily, was more acceptable to the patients than the usual INH-PAS combination.

4. Within six weeks, 40 per cent of the x-ray films showed evidence of improvement. The figure rose to 74 per cent in 12 weeks, and to 93 per cent of 48 subjects treated for six months.

5. Evidence of reduction in the bacillary content of the sputum was

TABLE IV
CYCLOSERINE COMBINATION THERAPY
PULMONARY TUBERCULOSIS
Bacteriological Status
Initially all sputa were strongly positive on smear and culture

	Period (Months)				
Degree of Change	1½	3	6	9	12
Negative	37	51	29	10	6
Positive	38	13	6	4	0
Pending	6	10	13*	7*	2*
TOTAL	81	74	48	21	8

*All of these were negative on culture previously.

obtained within six weeks of treatment. Within three months, 80 per cent of 64 sputa were negative on culture, and at six months the figure rose to 87 per cent.

6. Bacillary sensitivity to cycloserine fell slowly and slightly during prolonged treatment with the larger doses. From 0.5 Gm. of cycloserine per day, there was no evidence of decreased sensitivity.

7. Resistance to INH developed during the administration of the cycloserine isoniazid combination at approximately the same rate as is seen when INH is given alone.

8. It is our conclusion that a combination of 0.25 Gm. of cycloserine and 0.15 Gm. of INH given twice daily is effective and safe therapy against previously untreated cases of pulmonary tuberculosis. We feel that our clinical results were superior to the usual INH-PAS therapy, both in speed and degree of response, as gauged by x-ray film changes and sputum conversion.

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RESUMEN Y CONCLUSIONES

1. Se trataron casos nuevos sin haber recibido previamente otro tratamiento, con la asociación de cicloserina-isoniacida, oralmente.

2. Se han tratado ochenta y un casos por seis a 16 meses con sólo una reacción que no necesitó interrupción del tratamiento.

3. Mejoría clínica, reducción de la fiebre, disminución del volumen de los esputos, y aumento de peso, fué lo que ocurrió en todos los casos. Además, la administración de una sola capsula conteniendo cicloserina e isoniacida, dos veces al día, fué más aceptable para los enfermos que la combinación habitual de PAS-HAIN.

4. Dentro de seis semanas el 40 por ciento mostraron mejoría radiológica evidente. Subió la proporción a 74 por ciento a las 12 semanas y a 93 por ciento de 48 sujetos tratados por seis meses.

5. Se logró evidencia de reducción del contenido bacilar de los esputos dentro de seis semanas. Dentro de tres meses, 80 por ciento de 64 esputos fueron negativos al cultivo, y a los seis meses subió a 93 por ciento.

6. La sensibilidad bacilar a la cicloserina cayó lenta y ligeramente durante tratamiento prolongado a altas dosis. Usando 0.5 de cicloserina por día, no se observó decrecimiento de la sensibilidad.

7. La resistencia a la HAIN se observó durante la administración de cicloserina-HAIN en la misma proporción que ocurre con la isoniacida sola.

8. Concluimos que una combinación de 0.25 de cicloserina y 1.15 Gm. de HAIN dados dos veces al día, es un tratamiento seguro y efectivo contra los casos nuevos de tuberculosis. Creemos que nuestros resultados son superiores a los logrados con PAS/HAIN usual tanto en rapidex como en grado de respuesta según puede estimarse por el aspecto radiológico y la conversión de esputos.

RESUME

1. Des formes de tuberculose pulmonaire récente, sans traitement préalable, furent traitées par l'association cyclosérine-isoniazide administrée par voie buccale.

2. 81 cas ont été traités de six à 16 mois, avec une seule réaction qui ne nécessita pas la cessation du traitement.

3. L'amélioration clinique, l'abaissement de la fièvre, la diminution du volume de l'expectoration et le gain de poids corporel survinrent rapidement dans chaque cas. En outre, l'administration d'une seule capsule contenant la cyclosérine et l'isoniazide, deux fois par jour, fut acceptée davantage par les malades que l'association habituelle isoniazide-P.A.S.

4. Au bout de six semaines, 40% des films radiologiques montrèrent une amélioration évidente. Le chiffre s'éleva à 74% pour 12 semaines, et à 93% chez 48 malades traités pendant six mois.

5. La preuve de la réduction du contenu bacillaire de l'expectoration fut obtenu en six semaines de traitement. En trois mois, 80% de 64 expectorations furent négatives à la culture, et au bout de six mois, le chiffre s'éleva à 93%.

6. La sensibilté des bacilles à la cyclosérine s'atténua lentement et faiblement pendant le traitement prolongé avec des doses plus élevées. Pour 0,5 mmgr. de cyclosérine par jour, il n'y eut aucune mise en évidence d'une diminution de la sensibilité.

7. La résistance à l'isoniazide, développée pendant l'administration de l'association de la cyclosérine-isoniazide, est approximativement la même que celle constatée lorsque l'isoniazide est donnée seule.

8. L'auteur conclut que l'association de 0,25 g. de cyclosérine et de 1,15 g. d'isoniazide donnée deux fois par jour est un traitment efficace et sans danger pour les nouveaux cas de tuberculose pulmonaire. Il croit que ses résultats cliniques furent supérieurs à ceux obtenus avec la thérapeutique habituelle par l'isoniazide-P.A.S., à la fois pour la rapidité de la réponse au traitement et son degré, comme le prouvent les modifications radiologiques et la négativité de l'expectoration.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNG

1. Es wurden frische, zuvor unbehandelte Fälle von Lungentuberkulose mit einer per os gegebenen Kombination von Cykloserin-INH-Kombination behandelt.

2. Es wurden 81 Fälle zwischen 6 und 16 Monaten behandelt mit nur einer einzigen Nebenwirkung, die jedoch keine Unterbrechung der Behandlung notwendig machte.

3. Klinische Besserung, Herabsetzung des Fiebers, Verringerung der Auswurfmenge und Gewichtszunahme traten prompt in jedem Falle ein. Zusätzlich war die Verabfolgung einer einzelnen Kapsel mit Cykloserin und INH 2-mal täglich für den Patienten besser zuträglich, als die gewöhnliche INH-PAS-Kombination.

4. Innerhalb von 6 Wochen zeigten 40% der Röntgenaufnahmen einen

Anhalt für eine Besserung. Die Ziffer stieg bis auf 74% in 12 Wochen und auf 93% bei 48 Personen die 6 Monate lang behandelt wurden.

5. Ein Anhalt für die Hersetzung des Bazillengehaltes des Sputums liess sich innerhalb von 6 Behandlungswochen erreichen. Innerhalb von 3 Monaten waren 80% von 64 Sputen kulturell negativ und in 6 Monaten stieg diese Ziffer bis auf 93%.

6. Die bakterielle Sensibilität auf Cykloserin ging langsam und leicht zurück während lang anhaltender Behandlung mit grösseren Dosen. Bei 0,5 Cykloserin täglich fand sich kein Anhalt für eine Herabgesetzte Sensibilität.

7. INH-Resistenz entwickelte sich während der Anwendung der Cykloserin-INH-Kombination in ungefähr der gleichen Häufigkeit, wie man sie sieht, wenn INH allein gegeben wird.

8. Es ist unsere Folgerung, dass eine Kombination von 0,25 Cykloserin und 1,15 INH, 2-mal täglich gegeben, eine wirksame und sichere Therapie ist bei neuen Fällen von Lungentuberkulose. Wir haben den Eindruck, dass unsere klinischen Ergebnisse der gewöhnlichen INH-PAS-Behandlung überlegen sind, sowohl im Tempo wie im Grad der Antwort, wie sich schätzen lässt aus den röntgenologischen Veränderung und dem Negativ-Werden des Sputums.

REFERENCES

1 Hidy, P. H., Hodge, E. B., Young, V. V., Harned, R. L., Brewer, G. A., Phillips, W. F., Runge, W. F., Stavely, H. E., Pohland, A., Boaz, H. and Sullivan, H. R.: "Structure and Reaction of Cycloserine," *J. Am. Chem. Soc.*, 77:2345, 1955.

2 Jones, L. R.: "Colorimetric Determination of Cycloserine, a New Antibiotic," *Analytical Chemistry*, 28:39, 1956.

3 Nair, K. G. S., Epstein, I. G., Baron, H. and Mulinos, M. G.: "Absorption, Distribution, and Excretion of Cycloserine in Man," *Antib. Annual*, 1955-56.

4 Morton, R. F., McKenna, M. H. and Charles, E.: "Studies on the Absorption, Diffusion, and Excretion of Cycloserine," *Antib. Annual*, 1955-56.

5 Welch, H., Putnam, L. E. and Randall, W. A.: "Antibacterial Activity and Blood and Urine Concentrations of Cycloserine, a New Antibiotic, Following Oral Administration," *Antib. Med.*, 1:72, 1955.

6 Lillick, L., Strang, R., Boyd, L. J., Schwimmer, M. and Mulinos, M. G.: "Cycloserine in the Treatment of Nontuberculous Infections," *Antib. Annual*, 1955-56.

7 Harned, R. L., Hidy, P. H. and LaBaw, E. K.: "Cycloserine, I—A Preliminary Report," *Antib. and Chemo.*, 5:204, 1955.

8 Herrold, R. D., Boand, A. V. and Kamp, M.: "The Treatment of Stubborn Urinary Infections with a New Antibiotic: Cycloserine," *Antib. Med.*, 1:665, 1955.

9 Epstein, I. G., Nair, K. G. S. and Boyd, L. J.: "Cycloserine, a New Antibiotic, in the Treatment of Pulmonary Tuberculosis. A Preliminary Report," *Antib. Med.*, 1:80, 1955.

10 Cummings, M. M., Patnode, R. A. and Hodgins, P. C.: "Effects of Cycloserine on Mycobacterium Tuberculosis in Vitro," *Antib. and Chemo.*, 5:198, 1955.

11 Ravina, A., Pestel, M., Albouy, R. and Rey, M.: "Preliminary Clinical Report on Cycloserine in the Treatment of Tuberculosis," *Antib. Annual*, 1955-56.

12 Epstein, I. G., Nair, K. G. S. and Boyd, L. J.: "The Treatment of Human Tuberculosis with Cycloserine: Progress Report," *Dis. Chest*, 29:241, 1956.

13 Ibid.: "The Treatment of Human Tuberculosis with Cycloserine. A Year's Progress," *Antib. Annual*, 1955-56.

14 Robitzek, E. H. and Nenashev, P. K.: "Cycloserine and Isoniazid in Reduced Dosage Combination in the Therapy of Pulmonary Tuberculosis. A Preliminary Report," *Antib. Annual*, 1956-57.

15 Nair, K. G. S., Epstein, I. G. and LoBaido, F.: "The Toxicity of Cycloserine During the Treatment of Pulmonary Tuberculosis," *Trans. 16th VA-Armed Forces Con-*

ference on the Chemotherapy of Tuberculosis, St. Louis, Missouri, February 11-14, 1957.

16 Epstein, I. G., Nair, K. G. S. and Boyd, L. J.: "Treatment of Human Tuberculosis with Cycloserine Combined Therapy," *Trans. 15th VA-Army-Navy Conference on the Chemotherapy of Tuberculosis*, St. Louis, Missouri, February 6-9, 1956.

17 Wolinsky, E. and Steenken, W., Jr.: "Cycloserine Alone and in Combination with Other Drugs in Experimental Guinea Pig Tuberculosis," *Am. Rev. Tuberc.*, 75:510, 1957.

18 Trans. 14th VA-Army-Navy Conference on the Chemotherapy of Tuberculosis, Atlanta, Georgia, February 7-10, 1955, p. 509.

19 Moyer, R. E. and Schwartz, W. S.: "Development of Bacterial Resistance to Cycloserine and Its Correlation with Clinical and X-ray Changes," *Trans. 15th VA-Army-Navy Conference on the Chemotherapy of Tuberculosis*, St. Louis, Missouri, February 6-9, 1956, Table III, p. 381.

20 Cummings, M. M.: "Cycloserine: Resistance Data," *Trans. 15th VA-Army-Navy Conference on the Chemotherapy of Tuberculosis*, St. Louis, Missouri, February 6-9, 1956.

21 Russell, W. F., Jr. and Middlebrook, G.: "Persistent Excretion of Isoniazid-Susceptible Tubercle Bacilli," *Trans. 15th VA-Army-Navy Conference on the Chemotherapy of Tuberculosis*, St. Louis, Missouri, February 6-9, 1956.

22 Schwartz, W. S. and Moyer, R. E.: "Isoniazid Alone: A Follow-up of Results Obtained in Early 1952," *Trans. 14th VA-Army-Navy Conference on the Chemotherapy of Tuberculosis*, Atlanta, Georgia, February 7-10, 1955, pp. 62-64.

23 Robinson, H. J.: "The Pharmacology of Cycloserine (Oxamycin)," *Trans. 15th VA-Army-Navy Conference on the Chemotherapy of Tuberculosis*, St. Louis, Missouri, February 6-9, 1956.

24 Trans. 15th VA-Army-Navy Conference on the Chemotherapy of Tuberculosis, St. Louis, Missouri, February 6-9, 1956, p. 349.

25 Epstein, I. G., Nair, K. G. S. and Boyd, L. J.: "Cycloserine Combined with Other Antituberculous Agents in the Treatment of Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 75:553, 1957.

26 Murray, F. J.: "A Pilot Study of Cycloserine Toxicity," *Am. Rev. Tuberc.*, 74:196, 1956.

27 Storey, P. B., Duvall, R. C. and McLean, R. L.: "The Convulsive Effect of Cycloserine," *A.M. & C.T.*, 3:258, 1956.

28 Storey, P. B. and McLean, R. L.: "Some Considerations of Cycloserine Toxicity," *Am. Rev. Tuberc.*, 75:514, 1957.

29 Mulinos, M. G.: "Cycloserine: An Antibiotic Paradox," *Antib. Annual*, 1955-56.

30 Prescott, B., Kauffmann, G. and James, W.: "Increase in Tolerated Dose of Isoniazid in Mice by Use of Cycloserine," *Proc. Soc. Exper. Biol. & Med.*, 94:94, 1957.

31 Schmidt, L.: Trans. 15th VA-Army-Navy Conference on the Chemotherapy of Tuberculosis, St. Louis, Missouri, February 6-9, 1956.

32 Anderson, R. C., Worth, H. M., Welles, J. S., Harris, P. N. and Chen, K. K.: "Pharmacology and Toxicology of Cycloserine (Seromycin)," *Trans. 15th VA-Army-Navy Conference on the Chemotherapy of Tuberculosis*, St. Louis, Missouri, February 6-9, 1956.

Artificial Pneumothorax as an Aid to Chemotherapy in the Treatment of Pulmonary Tuberculosis*

A. F. FOSTER-CARTER, D.M. (OXON)**
Frimley, England

Twenty years ago, when the writer joined the staff of the Brompton Hospital in London, approximately half the tuberculous patients were having artificial pneumothorax (A.P.) treatment. During the next 10 years there was a slow decline in the use of this method and in the past five years that decline has become more rapid. Figure 1 (Table I) shows the percentage of patients discharged from the Brompton Hospital Sanatorium at Frimley over the past six years who had unilateral A. P. treatment. In 1950 A. P. was attempted in 4 per cent and kept up in 31 per cent, while in 1956 it was attempted in 8 per cent and maintained in only 3 per cent. As most of the patients in this Sanatorium are under the care of physicians on the staff of the Brompton Hospital, these figures reflect the views of a representative group of British Chest Physicians. Individual opinions of course vary considerably; all would agree that A.P. now only has a limited place in the treatment of pulmonary tuberculosis but some have gone further and have ceased to use the method altogether. It is the purpose of this paper to assess the present position and attempt to decide which of these views is right.

Historical Survey

It may help to clarify our ideas if we survey briefly the vicissitudes of A.P. treatment in the past 20 years. At first the selection of cases was poor, with the result that many unsatisfactory pneumothoraces were induced and maintained and the complication rate was high. Gradually the principles underlying successful collapse therapy became apparent, particularly the need for effective relaxation of the diseased area. But, as so often happens, the pendulum swung too far; the pursuit of the free lung became almost a fetish and few patients escaped thoracoscopy. Cauterisation of adhesions is a procedure which has a considerable morbidity rate and thus another source of complications was introduced.

Ten years ago, A.P. treatment was still the subject of much discussion, although it was extensively employed. There was no general agreement on the results achieved and many of the published statistics were fallacious (Bloch, Tucker and Adams[1]). Also it had a bad reputation for complications, particularly among thoracic surgeons who so often had to deal with disasters following the use of A.P. in unsuitable cases. In fact the memory of these bad old days still lingers, or has been handed down as hearsay to those too young to remember, and thus it colours our attitude to A. P. treatment even today.

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**From the Brompton Hospital Sanatorium, Frimley, Surrey, England.

In 1949 an investigation was started at the Brompton Hospital Sanatorium in an attempt to discover the prognosis of patients with cavitated disease treated by A.P., and also the effect of anatomically perfect or imperfect collapse on the prognosis. The results of this investigation were published in 1952 (Foster-Carter, Myers, Goddard, Young and Benjamin,[2] Foster-Carter[3]) by which time antibacterial treatment was firmly established and the indications for A. P. were getting fewer. Nevertheless, the findings still have considerable relevance and will be considered briefly. During the years 1937 to 1942, 442 patients were discharged from the Sanatorium with unilateral A. Ps. All these patients had cavitated disease and all were followed for a minimum of eight years, with an average of five years' observation after termination of

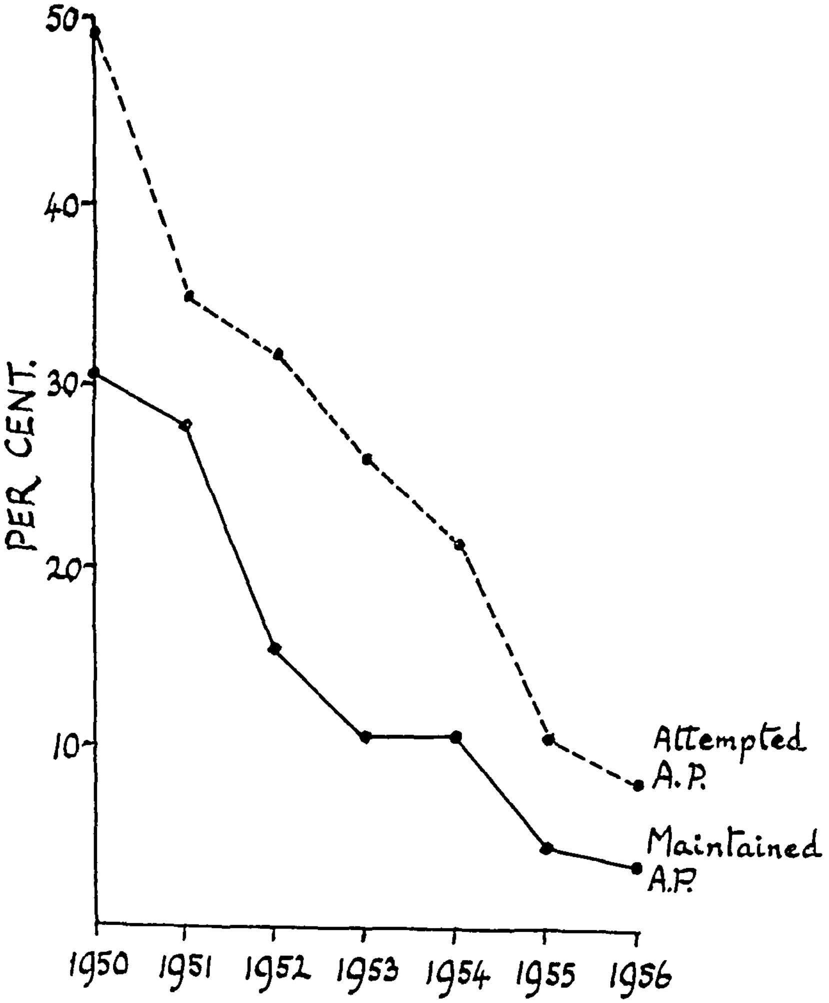


FIGURE 1: Graph showing the percentage of patients discharged from the Brompton Hospital Sanatorium during the past six years who had unilateral A. P. treatment. Continuous line: A. P. maintained. Dotted line: A. P. attempted (see Table I).

A.P. treatment; only just over 1 per cent were lost from observation. Some of the more important findings are shown graphically in Figure 3. The radiological grouping will be seen to correspond closely with the American National Tuberculosis Association classification and, since the initial extent of the disease is the most important single prognostic factor, great care was taken to see that groups were truly comparable in this respect. It will be seen that when cavity closure was achieved the results were good, regardless of the presence or absence of adhesions. In 230 patients with initial cavitation, most of whom had moderately advanced disease, the eight year survival rate was 90 per cent; a high figure considering that none of these patients had chemotherapy. When the A.P. failed to close the cavity the result was almost always bad;

TABLE I

PATIENTS DISCHARGED FROM BROMPTON HOSPITAL SANATORIUM 1950-1956: SHOWING FREQUENCY OF DIFFERENT FORMS OF TREATMENT

Year	1950		1951		1952		1953		1954		1955		1956	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Number of Patients	332	100	328	100	335	100	272	100	309	100	357	100	341	100
Number having Chemotherapy	165	50	243	75	291	87	254	94	305	99	357	100	341	100
Unilateral A. P.	102	31	96	28	58	17	31	11	38	12	14	4	11	3
Bilateral A. P.	14	4	15	5	2	0.6	3	1	1	0.3	....	....	....	....
Unsuccessful A. P.	46	28*	35	24*	46	43*	37	51*	30	44*	26	65*	16	59*
Total A. P. Attempted	162	49	116	35	106	32	71	26	69	22	40	11	27	8
Pneumoperitoneum	87	26	63	19	62	18	31	11	21	7	29	9	16	5
Resection	22	7	21	6	41	12	44	16	44	14	53	15	47	14
Thoracoplasty	36	11	21	6	40	12	32	12	25	8	31	9	18	5
Apicolysis with Plombage	12	4	11	3	25	7	28	10	18	6	19	5	6	2
No Active Treatment	59	18	101	31	107	32	103	38	162	52	211	59	243	71

*Per cent of all A. P's attempted.

of 113 such patients only 36 per cent survived eight years. The incidence of complications followed the same pattern; when cavity closure was obtained, the incidence of effusion was 25 per cent and of empyema 11 per cent; these figures were not affected by the presence or absence of adhesions. Of the patients who had persistent cavities no less than 36 per cent developed empyemas and half of these died.

Although none of the patients in this investigation had chemotherapy, the results are important for several reasons. They show that the bad reputation attached to A. P. in some quarters is due to poor selection of cases in the past and is undeserved; in fact, when used rightly, A. P. achieves remarkably good results. They show that cavity closure and not absence of adhesions is the key to successful A.P. treatment; adhesions which do not prevent cavity closure have no effect on the prognosis and do not increase the complication rate. Finally they provide a yardstick against which we can measure the achievements of the anti-

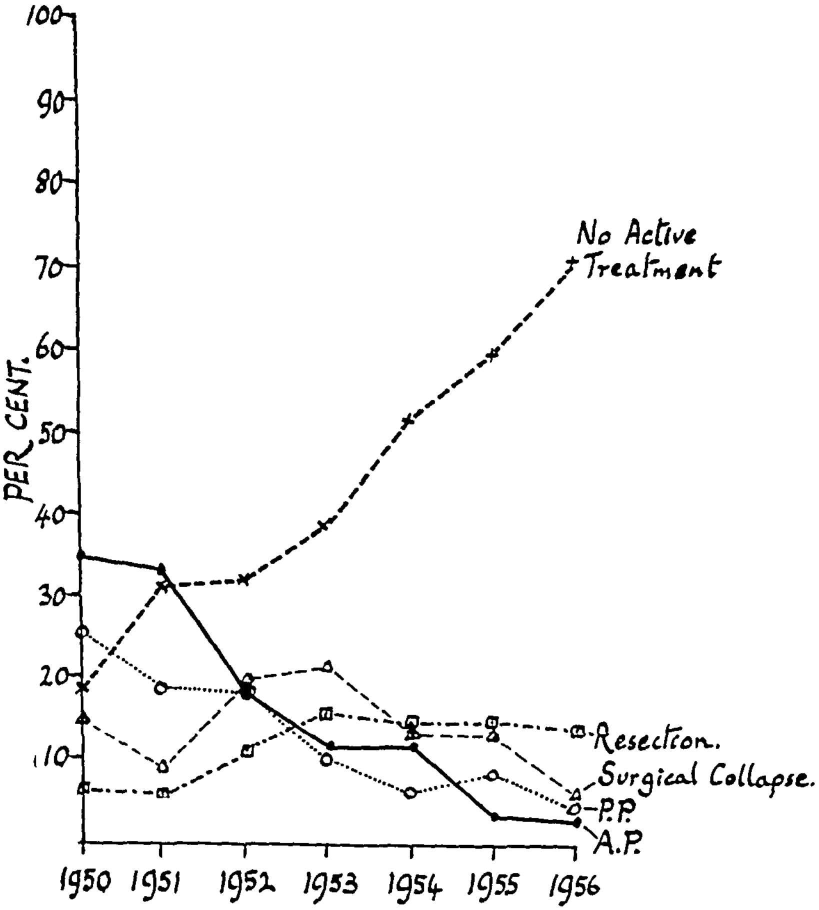


FIGURE 2: Graph showing the various forms of treatment undergone by patients discharged from the Brompton Hospital Sanatorium during the past six years (see Table I).

bacterial drugs in increasing the safety and efficiency of A.P. treatment today.

The Results of A.P. Treatment Combined with Chemotherapy

Evidence is steadily accumulating to show that modern chemotherapy has freed A.P. treatment from most of its former disadvantages (Birath,[4, 5] Scadding,[6] Dixon,[7] Thompson[8]). All authors agree that tuberculous empyema no longer occurs and that the incidence of pleurisy is reduced. This means that good functional results can be obtained in the vast majority of cases; Thompson[8] recorded marked pleural thickening in only 13 per cent of his patients while Birath[5] claims that if pleurisy is treated by rapid expansion of the lung, there is negligible loss of function in 95 per cent of cases.

Our own figures from the Brompton Hospital Sanatorium confirm these findings and suggest that still better results are being obtained as the duration of chemotherapy increases (Tables II and III). During the past six years there were discharged from this Sanatorium 174 patients who had been treated with chemotherapy and who also had established unilateral A. Ps. It will be seen from Table II that the duration of chemotherapy steadily increased throughout the series so that the later cases are not strictly comparable with the earlier ones. Quite apart from this, there are so many variable factors in pulmonary tuberculosis that any statistical assessment of the ultimate results of treatment would be unjustifiable on so small a series. Nevertheless all these patients have been followed up to the present time and their after-histories do enable us to decide whether the treatment achieved its immediate object and to assess the early complications.

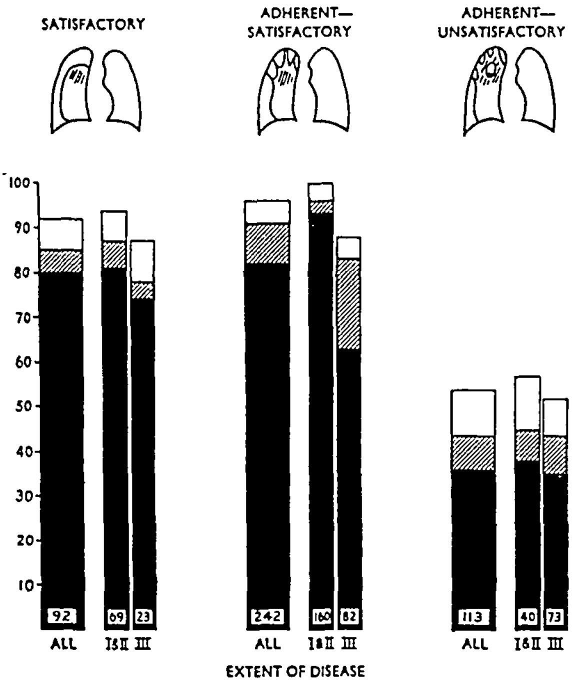
Most commonly, A.P. was used to control cavitation and it succeeded in all cases. This was to be expected because it has become the practice to abandon any A.P. which is not producing cavity closure. Initial cavi-

TABLE II

TYPE AND DURATION OF CHEMOTHERAPY GIVEN DURING THE YEARS 1951-1956

Year	Type of Chemotherapy	Average Duration
1951	SM and PAS	3 Months
1952	SM and PAS	3 to 4 months
1953	SM and PAS Occasional INH	3 to 4 months
1954	SM, PAS and INH in various combinations	6 to 9 months Occasional long-term
1955	SM, PAS and INH in various combinations	9 to 12 months +
1956	SM, PAS and INH in various combinations	9 to 12 months +

tation was present in 122 patients, all had closed their cavities by the time of their discharge from Sanatorium and this was confirmed by tomography in most cases. In only four instances was there evidence of a cavity re-opening during the period of observation (Table III). Seventeen of the 174 patients relapsed (10 per cent), but most of these were treated in the earlier years when the duration of chemotherapy was short; in only eight was there evidence of fresh activity in the treated lung. There were two deaths, one following spontaneous pneumothorax in a patient who had an extensive contralateral thoracoplasty and one from gastric carcinoma. Apart from pleurisy, only seven patients had other complications; one was the spontaneous collapse already mentioned, the others were comparatively minor and comprised two other spontaneous pneumothoraces, a premature obliteration, and three



From Foster-Carter et al. (1952), by permission of Brompton Hospital Reports

The number at the foot of each column is the number of cases in that group.

Extent of disease is shown in roman numerals:
I: one zone involved
II: two or three zones involved
III: four or more zones involved

Survival rates are shown as percentages:
☐ *survival for 3 years*
survival for 5 years
■ *survival for 8 years*

FIGURE 3: Survival of 442 unilateral A. P. cases before chemotherapy. *Satisfactory*—Free lung from start of A. P. or after adhesion section; cavities closed. *Adherent-Satisfactory*—Adhesions over diseased area which were not divided but cavities closed. *Adherent-Unsatisfactory*—Adhesions over diseased area but cavities did not close.

intrapleural haemorrhages only one of which was large enough to necessitate termination of the A.P.

No case of empyema occurred in this series but pleural effusion was still the most common complication; the total incidence was 17 per cent, which is much better than the 25 per cent found in our earlier series but is still of some consequence. Dixon[7] reported a similar incidence of effusion (20 per cent) in A.P. patients who had chemotherapy, whereas Thompson[8] and Birath[9] gave somewhat lower figures (11 per cent and 5 per cent respectively, although Birath's report only covered the first six months of treatment). Scadding[6] recorded only three transient, small effusions in 29 patients. The longer duration of chemotherapy in recent years has not been accompanied by a marked decrease in the number of effusions (Table III): Most of the patients who developed fluid did so in the first year and while still receiving antibacterial treatment. The effusions were usually small and transient; of the 174 A.P.s only 15

TABLE III

A. P. PATIENTS DISCHARGED FROM BROMPTON HOSPITAL SANATORIUM 1951-1956 WHO WERE TREATED WITH CHEMOTHERAPY

YEAR	1951	1952	1953	1954	1955	1956	TOTAL	
Minimum Follow-Up	5 Years	4 Years	3 Years	2 Years	1 Year	6 Months	Number	Per Cent
Number of A. P.'s	43	41	27	37	15	11	174	100
With Cavity	32	26	13	27	14	9	121	70
Sputum Culture + on Discharge	5	1	1	2			9	6
Cavity Opened Again Later	2		1	1			4	3
No Cavity	11	15	14	10	1	2	53	30
A. P. Terminated	40	30	24	33	4		131	75
Because of Effusion	3	4	3	3	2		15	9
A. P. Maintained	3	11	3	4	11	11	43	25
Relapsed	10	3	2	2			17	10
Effusion	7	9	5	6	3		30	17
Within One Year	6	6	3	4	3		22	13
After One Year	1	3	2	2			8	4
Other Complications	2		2	2	1		7	4
Died	1	1					2	1
Well at End of Follow-Up	41	39	25	35	14	11	165*	95

*Of the nine patients not known to be well at the end of the observation period, two had died; one had recently relapsed; six were well up to one year ago but final news not yet received.

(9 per cent) had to be terminated because of persistent fluid. It seems possible that while some effusions are due to tuberculosis, others may be the result of a foreign body reaction in the pleura; the former would be reduced by chemotherapy whereas the latter would not. It may be significant that Birath[4] reported an incidence of only 5 per cent of "spontaneous" effusions in his patients compared with 15 per cent in those who had adhesions divided.

In recent years there has been a growing tendency to terminate without undue delay any A.P. which is not achieving its object. Table I shows that in 1950 only 28 per cent of all A.Ps. attempted were rejected as unsatisfactory, while in 1956 that figure had more than doubled. Because of this careful selection the functional results are now excellent and, as Thompson[8] has pointed out, they compare favourably with those following resection. Even a tendentious comparison made by Fleming[10] between old A.P. patients who had no chemotherapy and a series of carefully prepared resection patients, all of whom received antibacterial drugs, failed to show more than a slight difference in function between the two groups.

The Present Position

In view of the excellent results of modern A.P. treatment it may well be asked why the use of the method has declined to the extent shown in Figure 1. The most important reason is that the majority of the patients who would have been regarded as ideal subjects for A.P. treatment five years ago, now recover with antibacterial treatment and rest alone. A clear indication of the paramount position being achieved by chemotherapy will be seen in Table I (Figure 2), which shows that the percentage of patients receiving no "active" treatment has increased from 18 per cent in 1950 to 71 per cent in 1956. This increase has been at the expense of all other forms of treatment, but particularly A. P. and pneumoperitoneum. The latter procedures were used mainly to control small localised lesions with minimal cavitation and these are just the lesions which respond well to chemotherapy. More severe lung damage still requires surgical intervention, but the number of operations is not increasing and will probably decline as the antibacterial drugs are used for longer periods.

Contemporary Indications for A.P. Treatment

We may safely assume that in future all patients will have at least three months' initial treatment with antibacterial drugs, after which candidates for A.P. treatment will be selected from the relatively small number whose response to chemotherapy is not satisfactory. With this proviso, the main indications for A.P. treatment are:

1. Localised disease with cavitation.
2. Localised cavitation with widespread disease throughout the lung.
3. Localised cavitation in one lung when there is serious disease requiring surgical collapse in the other.

FIGURE 4

FIGURE 5

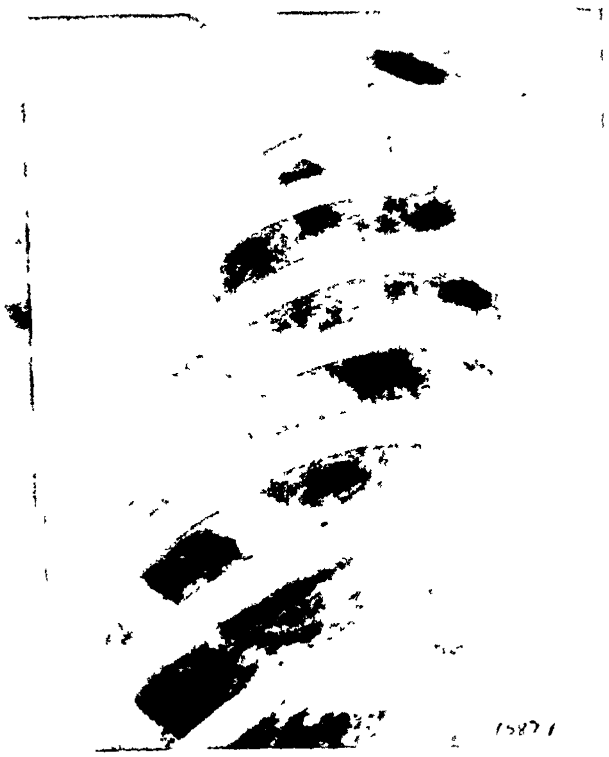


FIGURE 6

Figure 4: Man aged 29. Infiltration and a cavity in right in upper lobe.—*Figure 5:* Same patient after three and one-half months' chemotherapy. Cavity smaller but persisting.—*Figure 6:* Same patient after right A.P. Apical adhesions but cavity closed.

4. Localised cavitation in one lung when the other has virtually been put out of action by extensive surgery.

It is assumed that in all cases the cavitation is persisting and has ceased to improve, in spite of adequate chemotherapy.

Localised disease with cavitation is, in our experience, by far the most common indication for A.P. treatment at the present time. The situation in which it arises can best be illustrated by a short protocol:

G. C. Man, aged 29. A Veterinary Surgeon. Admitted to hospital in January 1956; sputum positive for tubercle bacilli; early tuberculous laryngitis; x-ray film showed infiltration and a cavity in the right upper lobe (Figure 4). May 1956, after three and one-half months' rest with daily streptomycin, INH and PAS: cavity smaller but still present and showing no sign of further diminution (Figure 5). Right A.P. induced; a few apical adhesions present but cavity closed and sputum converted within a month (Figure 6). September 1956, returned to full work. May 1957, still having chemotherapy; tomographs confirm cavity closure and resolution of lesions; A.P. treatment to be terminated.

In order to realise the advantages of A. P. treatment in such a case as this, let us consider the alternatives:

First: Continuation of antibacterial therapy alone. This may well succeed in the end, but it often takes many months. In the case under consideration the patient, who was a junior partner in a busy practice, was most anxious to get back to his work. He could not have been permitted to do so while he still had a cavity and positive sputum. No other form of treatment would have enabled him to return to work in so short a time.

Second: Resection. This is a major operation with an appreciable morbidity and a small mortality. Not infrequently the surgeon finds that he has to remove more of the lung than was originally estimated and this may necessitate a small thoracoplasty in addition. A.P., in contrast, is essentially a temporary and reversible procedure which leaves the lung

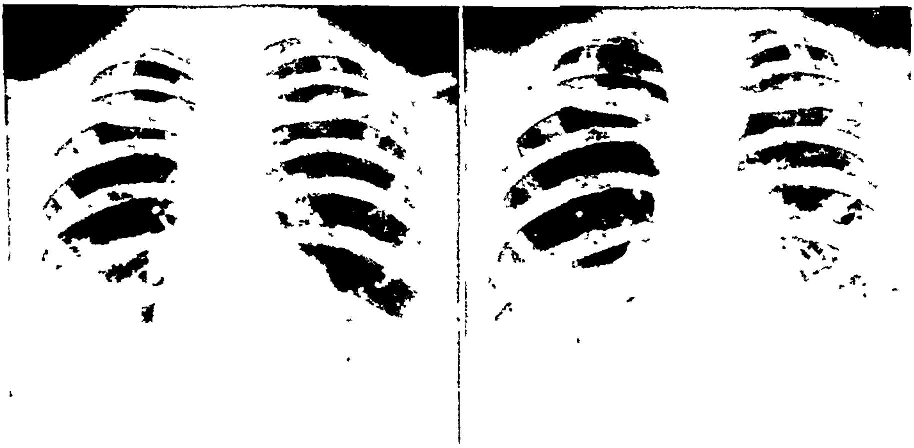


FIGURE 7 FIGURE 8

Figure 7: Woman aged 22. After three months' chemotherapy. Extensive infiltration right middle and lower lobes with a persistent cavity in middle lobe. Patient anxious to avoid operation.—*Figure 8:* Same patient two months later after right A. P.

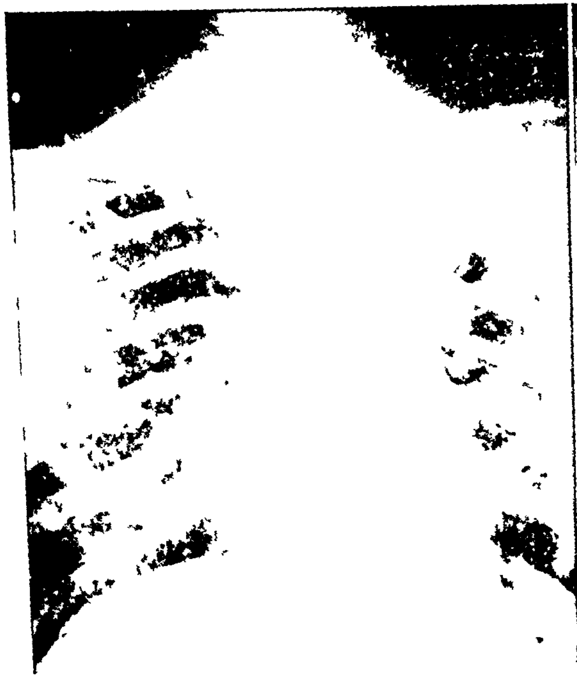


FIGURE 9

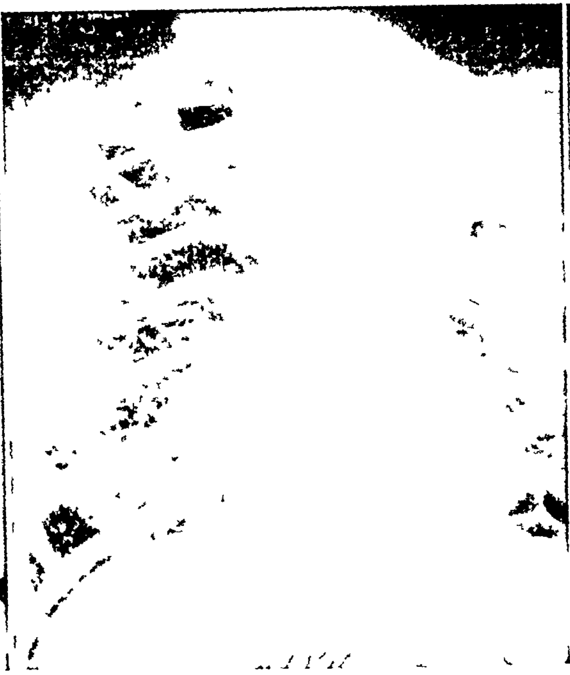


FIGURE 10

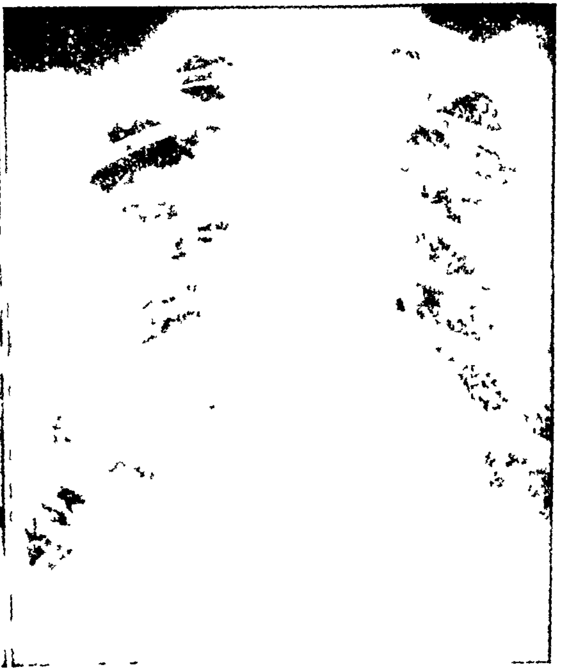


FIGURE 11

Figure 9: Man aged 33. After six months' chemotherapy. Sputum positive. Infiltration right upper lobe with cavity. Collapse and consolidation with cavitation left upper lobe and infiltration with small cavity in apex of left lower lobe.—*Figure 10:* same patient after right A.P. Apical adhesions but cavity closed.—*Figure 11:* Same patient after left upper lobectomy. Sputum negative. Disease in left lower lobe healing.

intact and should give a functional result equal, and often superior to, that following resection. There is nothing to be lost in attempting pneumothorax because if it is not satisfactory a resection can still be performed. Another less important but very practical advantage of A.P. treatment is that it avoids the ugly scar of a surgical operation; a benefit much appreciated by young women.

Third: Pneumoperitoneum. The pulmonary relaxation obtained by this method is limited, unless it is accompanied by temporary phrenic interruption, and there is a growing disinclination to use this combination because of the danger of permanent diaphragmatic paralysis. The concentric relaxation obtained by a satisfactory A.P. is much more effective than that produced by a pneumoperitoneum alone. The latter still has a limited use in the treatment of patients with widespread disease who are not responding to chemotherapy and who are unsuitable for A.P. treatment or surgery.

Having examined the alternatives it will be seen that there is much to be said for trying A.P. treatment when one wishes to control a limited, cavitated lesion. A trial pneumothorax can do no harm; if it does not achieve its object it can be terminated without delay and little time will have been lost. If however it does control the disease satisfactorily, a good result may confidently be expected, the patient's return to work is accelerated, and a major surgical operation may well have been avoided.

The second indication—localised cavitation with widespread disease throughout the lung—is an extension of the first, but surgical treatment is no longer an easy alternative. Resection of the cavitated area is frequently followed by re-activation of one or more of the residual lesions: surgical collapse therapy may control apical cavitation but it cannot be used if the cavity is in the lower part of the lung (Figure 7). It seems rational to try A.P. treatment in these circumstances, because it not only promotes cavity closure but also relaxes the whole lung and thus assists the healing of the diffuse lesions, instead of subjecting them to added strain. A.P. has also been shown to be particularly successful in the treatment of cavities in the apex of the lower lobe (Crofton[11]).

The remaining two indications for A.P. treatment are much less commonly seen but deserve mention. The use of an A.P. to control localised cavitation in one lung before embarking on surgical measures to deal with more extensive disease in the other, will sometimes avoid the need for bilateral surgery (Figures 9 to 11). The temporary and reversible character of pneumothorax renders it particularly suitable in this situation where surgical treatment for both lungs might leave the patient a respiratory cripple. This applies also to the final indication; the use of A.P. to control a fresh, small cavitated lesion in the "good" lung of a patient who has lost the function of the other lung after extensive surgery. Here again a successful A.P. will control the disease without eventual loss of respiratory function when the pneumothorax is terminated (Figures 12 and 13). The great danger associated with A.P. when the function of the contralateral lung is grossly impaired is the occurrence of spontaneous pneumothorax. This complication is uncommon if the A.P. is skilfully managed, but the one death in our series was due to this cause. When confronted with a case of this type, the clinician has to weigh the possible risks of A.P. against the probable result of surgery and the decision may be difficult.

Contra-indications and Management

The contra-indications to A.P. treatment are still very much the same as they were before the advent of chemotherapy. It is essentially a temporary measure and should not be used if there is extensive lung destruction. Care should be taken to ensure that the patient is not suffering from tuberculous bronchial ulceration; signs of bronchitis or the presence of atelectatic areas or tension cavities usually contra-indicate A.P. treatment. Lastly, A. P. will not affect large solid tuberculous foci in the lung.

Having induced A.P., the success or failure of the treatment will be judged solely by its effect on cavitation. If cavity closure is not achieved within a reasonable time—say one month— the A.P. should be terminated. If however cavity closure does occur, then any adhesions which are presented may safely be left alone. In our opinion cauterisation of adhesions ought now to be abandoned. It is an operation which inevitably damages the pleura and is often followed by a troublesome effusion which is unlikely to respond to chemotherapy. Also the diminished use of A.P. is bound to reduce the number of surgeons having the necessary experience to undertake this operation, the success of which has always de-

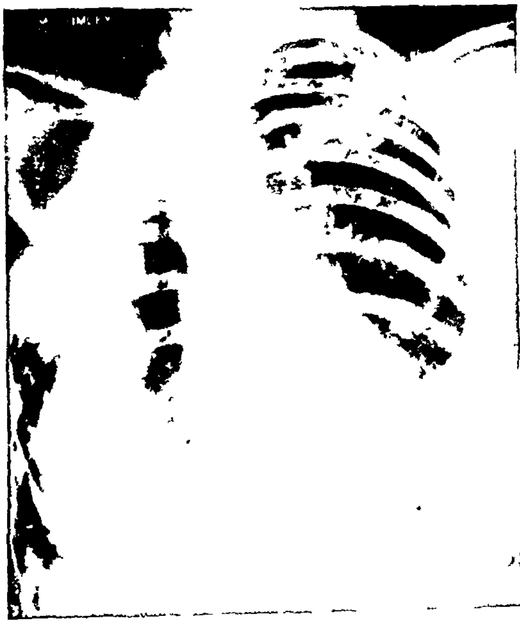


FIGURE 12

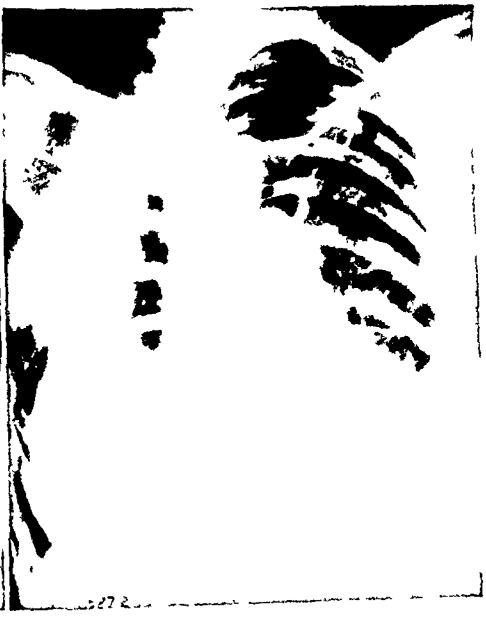


FIGURE 13

Figure 12: Woman aged 32. Right lung immobilised by old thoracoplasty followed by upper lobectomy and post-operative empyema. Cavity in left upper lobe. Sputum positive; unaffected by prolonged chemotherapy (Resistant to SM, INH and PAS).—*Figure 13:* Same patient after left A.P. Numerous apical adhesions but cavity closed and sputum negative.

pended so largely upon the skill of the operator. Therefore when adhesions are preventing cavity closure, it is probably best to abandon the A.P. forthwith in favour of some alternative method of treatment.

The condition of the pleura must be watched carefully if good function is to be preserved. Small effusions are harmless provided that the fluid does not rise above the diaphragm and that it absorbs in a few weeks. Large or persistent effusions demand energetic treatment, because they so often lead to pleural thickening and impairment of function. Rapid expansion of the lung is always indicated and may be achieved by the technique which Birath[9] has described. This includes postural treatment with the patient lying on the sound side, abdominal breathing exercises, and frequent pleural aspirations. We have not found the introduction of antibiotics into the pleural cavity to be advantageous or desirable.

The maintenance of A.P. also requires skill and experience and the best results are obtained when the patient is able to remain under the care of the same physician for the whole duration of the treatment (Young[12]). Formerly about three years was considered the best length of time to maintain an A.P., although slight disease was often treated for shorter periods. There is no doubt that the time can now be drastically reduced and 12 to 18 months is known to have been sufficient in many cases. It is highly probable that, with long-term chemotherapy, an even shorter duration of collapse would give satisfactory results. Before the days of antibacterial drugs it was not uncommon to see cavity closure achieved by an A.P. which was regarded as unsatisfactory and terminated after only a few weeks' duration. Cavities which close during antibacterial treatment seldom re-open and it now seems reasonable to try the effect of allowing the lung to expand quite soon after the A.P. has achieved its object. A great advance will have been made if it proves possible to obtain permanent cavity closure by means of pneumothorax which need be maintained only for the period of hospital treatment.

Conclusion

In conclusion it may be said that antimicrobial drugs have now assumed such a paramount position in tuberculosis therapy that all other forms of treatment, both medical and surgical, have become merely ancillary. Nevertheless artificial pneumothorax still has a small but important part to play in the treatment of patients whose response to chemotherapy is not entirely satisfactory, and short-term pneumothorax may well prove to be increasingly useful in promoting the rapid closure of cavities.

SUMMARY

Analysis of 174 patients, treated with unilateral pneumothorax and chemotherapy during the past six years, suggests that most of the former disadvantages of artificial pneumothorax have now disappeared; but it is also shown that more effective chemotherapy is reducing the need for artificial pneumothorax, in common with other forms of treatment.

Artificial pneumothorax still has a small but important role in treat-

ment; reasons are given why it is preferable to other types of therapy in certain situations.

It is suggested that the practice of cauterisation of adhesions is no longer necessary and should now be discontinued.

The duration of artificial pneumothorax can now be greatly reduced and the use of this treatment for short periods may prove to be valuable in promoting quick cavity closure.

RESUMEN

Un análisis de 174 enfermos tratados con neumotórax unilateral durante los últimos seis años, sugiere que la mayoría de las desventajas antes achacadas al neumotórax artificial ahora han desaparecido; pero también se ha mostrado que la quimioterapia más efectiva ahora, ha reducido la necesidad del neumotórax, así como otras formas de tratamiento.

El neumotórax tiene aún un papel pequeño pero importante en el tratamiento; se dan las razones de por qué es preferible a otros tipos de tratamiento en ciertas condiciones.

Se sugiere que la práctica de la cauterización de adherencias ya no es necesaria y ahora debe abandonarse.

La duración del neumotórax artificial puede ahora reducirse grandemente y el uso de este tratamiento por corto tiempo, puede ser valioso para producir el cierre pronto de las cavernas.

RESUME

L'étude de 174 malades, traités par pneumothorax unilatéral et chimiothérapie pendant les six années passëes, suggère que la plupart des inconvénients anciens du pneumothorax artificiel ont maintenant disparu; mais elle montre également que la chimiothérapie plus efficace est en voie de réduire la nécessité du pneumothorax artificiel ainsi que d'autres formes de traitement.

Le pneumothorax artificiel a encore un rôle, petit mais important dans le traitement. L'auteur donne les raisons pour lesquelles il est préférable à d'autres types de traitement dans certaines situations.

L'auteur suggère que la pratique de cautérisation des adhérences n'est plus nécessaire et devrait être abandonnée.

La durée du pneumothorax artificiel peut maintenant être beaucoup réduite et l'emploi de ce traitement pour de petites périodes de temps peut être tenu pour valable car il permet la fermeture rapide des cavernes.

ZUSAMMENFASSUNG

Die Analyse von 174 Patienten, die während der verflossenen 6 Jahre mit einseitigem Pneumothorax und Chemotherapie behandelt wurden, legt die Vermutung nahe, dass die meisten der früheren Nachteile des künstlichen Pneumothorax heute nicht mehr bestehen; es ist aber auch gezeigt worden, dass eine besser wirksame Chemotherapie die Notwendigkeit eines künstlichen Pneumothorax herabsetzt, ebenso wie auch anderer Behandlungsformen.

Der künstliche Pneumothorax besitzt noch eine geringe, aber wichtige

Bedeutung bei der Behandlung; es werden Gründe dafür angeführt, weshalb er in gewissen Situationen anderen Behandlungsarten vorzuziehen ist.

Es wird angenommen, dass die Praxis der Durchtrennung von Verwachsungen nicht länger erforderlich ist und jetzt aufgegeben werden sollte.

Die Dauer des künstlichen Pneumothorax kann jetzt auch beträchtlich verringert werden, und die Benutzung dieser Behandlung für kurze Zeit kann sich als wertvoll erweisen für die Begünstigung eines raschen Kavernenverschlusses.

Acknowledgments: My thanks are due to the Medical Committee of the Brompton Hospital, London, for permission to publish the statistics here recorded. I am also much indebted to Miss K. Colegate for her work on the follow-up and to Mr. D. Kemp for the x-ray reproductions.

REFERENCES

1 Bloch, R. G., Tucker, W. B. and Adams, W. E.: "Standards and Criteria in Artificial Pneumothorax Therapy," *J. Thoracic Surg.*, 10:310, 1941.

2 Foster-Carter, A. F., Myers, M., Goddard, D. L. H., Young, F. H. and Benjamin, B.: "The Results of Collapse and Conservative Therapy in Pulmonary Tuberculosis," *Brompton Hospital Reports*, 21:1, 1952.

3 Foster-Carter, A. F.: "Long-Term Results of Artificial Pneumothorax Treatment," *British Medical Bulletin*, 10:150, 1954.

4 Birath, G.: "The Initial Period of Artificial Pneumothorax," *Dis. Chest*, 24:245, 1953.

5 Birath, G.: "Pneumothorax stallning i dagens behandling av lungtuberkulos," *Svenska Lakt.*, 52:184, 1955.

6 Scadding, J. G.: "The Treatment of Pulmonary Tuberculosis," *Lancet*, 49, 99 and 154, 1955.

7 Dixon, W. M.: "Artificial Pneumonthorax in the Treatment of Pulmonary Tuberculosis," *Tubercle, London,* 38:21, 1957.

8 Thompson, B. C.: "Artificial Pneumothorax Under Chemotherapy," *Brit. J. Tuberc.*, 51:181, 1957.

9 Birath, G.: "Guided Symphysis—Functional Prophylaxis in Exudative Pleurisy and Pneumothorax Fluid," *Am. Rev. Tuberc.*, 66:134, 1952.

10 Fleming, H. A.: "Pulmonary Function Before and After Segmental Resection and After 'Ideal' Pneumothorax Treatment," *Brit. M. J.*, 1:485, 1957.

11 Crofton, J.: "Tuberculous Cavities in the Apex of the Lower Lobe," *Thorax*, 4:96, 1949.

12 Young, F. H.: "The Place of Artificial Pneumothorax in the Treatment of Pulmonary Tuberculosis," *Brompton Hospital Reports*, 18:56, 1949.

Coexistence of Fungi and Tubercle Bacilli*

LOUISE B. LONGO, M.S., ALICE B. HARBUCK, B.S.
and WALTER FLEISCHMANN, M.D., PH.D.**
Memphis, Tennessee

The presence of fungi in the sputa of newly admitted patients in a tuberculosis hospital has been investigated in order to determine the coexistence of fungi and tubercle bacilli in the lungs of patients with pulmonary tuberculosis. Larkin and Phillips[1] have reviewed the literature on coexistent pulmonary tuberculosis and fungal disease. These authors reported three cases of dual fungal-tuberculosis infection with a poor prognosis. Greer and Gemoets[2] have suggested a symbiotic relationship between tubercle bacilli and coexisting fungi. They noticed a tendency for pulmonary tuberculosis to develop a more devastating course when it is associated with an invasion of parasitic fungi. Mankiewicz[3] demonstrated a stimulating effect of Candida albicans on the growth of Mycobacterium tuberculosis, in vitro. Though the pathogenicity of this fungus is questionable, its occurrence in the sputum of patients with pulmonary tuberculosis is of general interest.

The media used for isolation of fungi were blood agar containing 40 micrograms penicillin G and 40 micrograms of streptomycin per ml.; Littman's oxgall agar containing 30 micrograms streptomycin per ml., and Sabouraud's glucose agar containing 40 micrograms of penicillin and 40 micrograms of streptomycin per ml. Blood agar supported growth in all isolations of Histoplasma capsulatum; Littman's medium did not support growth in any case while Sabouraud's medium supported growth in 50 per cent of the isolations of H. capsulatum.

All newly admitted patients were studied for a period of 11 months. Three separate sputum specimens were collected from each of 505 patients.

Tables I and II demonstrate the result of this investigation.

As indicated in Table IV, during this study four cases of unsuspected histoplasmosis were diagnosed. M. tuberculosis was not cultured from any one of these patients. Cryptococcus neoformans and Geotrichum candidum were coexistent with M. tuberculosis in one patient each. These findings suggest the advisability of frequent sputum cultures for fungi in a tuberculosis hospital.

Mankiewicz[3] studied the possible effect of Candida albicans on the growth of M. tuberculosis since the two organisms were frequently isolated from the same sputum. At this hospital the patient's response to therapy in cases of dual infection with Candida albicans and Mycobacterium tuberculosis is being investigated.

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*From the Laboratory Service, Veterans Administration Hospital.
**Presently at Mountain Home, Tennessee.

TABLE I

PATIENTS WITH SPUTA POSITIVE OR NEGATIVE FOR FUNGI

	Total	Per Cent
Total number of patients	505	100
With negative fungus cultures	277	54.8
With positive fungus cultures	211	41.8
With contaminated fungus cultures	17	3.4

TABLE II

INCIDENCE OF TYPES OF FUNGI

	Total	Per Cent
Total patients positive for fungus	211	100
Positive for Candida species	205	97.1
Positive for Cryptococcus neoformans	1	0.5
Positive for Geotrichum candidum	1	0.5
Positive for Histoplasma capsulatum	4	1.9

Yeast-like fungi were isolated in 40.6 per cent of the patients. Table III shows the incidence of positive and negative cultures for fungi and tubercle bacilli.

TABLE III

INCIDENCE OF POSITIVE AND NEGATIVE CULTURES FOR FUNGI AND TUBERCLE BACILLI

	Total	Per Cent
Total number of patients (except those with all cultures contaminated)	487	100
Negative for tubercle bacilli and fungi	85	17.5
Negative for tubercle bacilli, positive for fungi	74	15.2
Positive for tubercle bacilli and fungi	137	28.1
Positive for tubercle bacilli, negative for fungi	191	39.2

TABLE IV

INCIDENCE OF POSITIVE CULTURES FOR FUNGI ACCORDING TO SPECIES

Cultures Positive for Fungi	Culture for M. Tuberculosis Negative	Culture for M. Tuberculosis Positive
Candida albicans	57	100
Candida sp.	13	35
Cryptococcus neoformans	0	1
Geotrichum candidum	0	1
Histoplasma capsulatum	4	0

SUMMARY

The sputa of all newly admitted patients were cultured for fungi during a period of 11 months. Four cases of histoplasmosis were detected among 505 patients. M. tuberculosis was not cultured from any one of these. However, Cryptococcus neoformans and Geotrichum candidum were coexistent with M. tuberculosis in one patient each.

RESUMEN

Durante once meses se cultivaron los esputos de todos los enfermos ingresados buscando hongos en ellos. Se descubieron cuatro casos de histoplasmosis entre 505 enfermos. En ninguno de estos se cultivó la micobacteria tuberculosa. Sin embargo, el criptococcus neoformans y el geotricum candidum coexistieron con la micobacteria tuberculosa en un caso.

RESUME

Les expectorations de tous les malades nouvellement admis furent mises en cultures pour la recherche d'éléments mycosiques pendant une période de onze mois. Quatre cas d'histoplasmose furent découverts sur 505 malades. Dans aucun de ces cas le bacille tuberculeux ne fut décelé par culture. Cependant, des malades ont été observés chez qui coexistaient avec le bacille de Koch chez l'un le cryptococcus neoformans, chez l'autre le geotrichum candidum.

ZUSAMMENFASSUNG

Der Auswurf neu aufgenommener Patienten wurde während eines Zeitabschnittes von 11 Monaten kulturell auf Pilze verarbeitet. Es wurden 4 Fälle von Histoplasmose gefunden unter 505 Kranken. Bei keinem von diesen liess sich M.-tuberculosis kulturell gewinnen. Jedoch kamen Cryptococcus neoformans und Geothrichum candidum gleichzeitig mit M.-tuberculosis bei je einem Patienten vor.

REFERENCES

1 Larkin, J. C. and Phillips, S.: "Coexistent Pulmonary Tuberculosis and Fungal Disease," *Am. Rev. Tuberc.*, *72:667, 1955.*

2 Greer, A. E. and Gemoets, H. N.: "The Coexistence of Pathogenic Fungus in Certain Chronic Pulmonary Diseases, with Especial Reference to Pulmonary Tuberculosis," *Dis. Chest*, *9:212, 1943.*

3 Mankiewicz, E.: "Mycobacterium Tuberculosis and Candida Albicans: A Study of Growth Promoting Factors," *Canad. J. Microbiol.*, 1:85, 1954.

SECTION ON CARDIOVASCULAR DISEASES

The Correction of Mitral Insufficiency With a Trans-Valvular Polyvinyl Formalinized Plastic (Ivalon) Sponge Prosthesis*

A Preliminary Report

WILLIAM RAY RUMEL, M.D., F.C.C.P. and PRESTON R. CUTLER, M.D., F.C.C.P.
Salt Lake City, Utah

During the past half century a tremendous amount of work has been done in developing surgical methods to control mitral insufficiency. The pathological changes found in this disease, the disturbed physiology and the basic principles involved in the various corrective measures which have been used, have been well discussed in previous writings.[1-16] As a result of this work many phases of the problem are reasonably well understood and agreed upon. Experience has shown that the introduction of prostheses in general has produced rather discouraging results for a number of reasons. The same can be said for methods involving sutures placed near the edges of the opposing mitral leaflets. On the other hand, suture methods which bring about leaflet apposition by altering the contour or the size of the annulus fibrosus have produced definitely encouraging results.[8 14 15] In spite of this, the overall progress which has been made to date in solving the problem has not been sufficiently great as to dispel further attempts to develop better methods. The purpose of this communication is to give a preliminary report on a technique involving the introduction of a trans-valvular prosthesis which embodies certain established principles plus additional factors which seem to simplify the technical problem of correcting mitral insufficiency and may provide lasting beneficial results.

Background for Method

The introduction of foreign material or even autogenous tissues into the region of the mitral valve has been associated with a high incidence of early and late complications, some of which are poorly understood. Thrombi are prone to form on exposed sutures or irregular surfaces of most intracardiac foreign substances and may cause serious or fatal arterial embolization.[11 16 17] A hemorrhagic tendency not infrequently develops with diffuse oozing from all cut surfaces. This bleeding usually fails to respond to standard therapeutic measures. The cause of this state is not clear but

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*From the Department of Thoracic and Cardiovascular Surgery of The Latter-day Saints Hospital, Salt Lake City, Utah.
Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.

seems to be most troublesome when moveable foreign material is placed into the blood stream, especially if the mass comes into repeated contact with adjacent tissues causing trauma to the cellular elements of the blood.[5, 18] In addition to these complications, hemolysis of greater or lesser severity develops in a significant number of cases and is associated with the usual clinical and laboratory findings present when excessive erythrocyte destruction is present. Although careful studies have been reported recently[19] the overall problem is not well understood. The magnitude of these three complications alone has been sufficiently great so as to strongly deter the general clinical use of most types of prostheses.

In experimental animals the rarity of these complications, particularly those of thrombo-embolic nature when polyvinyl formalinized plastic sponge (Ivalon) prostheses were placed across the left ventricle between the mitral leaflets[7] or across the mitral valve from atrium to ventricle[13] immediately begs for an explanation. A likely one is that this plastic material becomes much like living tissue very soon after its introduction into the blood stream, due to the ingrowth of vascular fibrous tissue into the interstices of the sponge followed by the formation of a smooth, glistening surface covering which grossly and microscopically is indistinguishable from the adjacent endocardial tissue.[7 13 20 21] Most solid substances preclude such changes because of their inherent physical properties and even living autogenous or homogenous tissue transplants are apt to show early changes of non-viability with the inflammatory and thrombotic complications associated with this state. Implanted sponge has been shown to produce minimal inflammatory and necrotic changes in living tissue adjacent to it and only mild thickening of the valvular endocardium which comes in contact with it during valve closure.[7 13] In addition, it appears to maintain its size and much of its pliability in contrast to autogenous or homogenous tissues which generally swell, then shrink to a fraction of their original size.[7 10] In experimental animals intracardiac implantation has not been followed by complicating infections.[7 13] Regardless as to what theoretical or practical explanation is given, Ivalon seems to be well tolerated experimentally and also clinically by patients receiving intracardiac patches or aortic grafts. The rarity of complications seemed to justify further use of this material, particularly when its physical properties make it a very usable and adaptable substance in dealing with the technical problems involved in repairing an insufficient mitral valve. Its texture is soft so that a rough form made before the time of surgery can be shaped and trimmed readily at the operating table to fit the defect found between the mitral leaflets, regardless of its size and shape. This soft texture seems to allow it to become compressed and molded by the opposing cusps so as to fit the exact contour of their firm, irregular edges. Its workable characteristics make it possible to fashion a prosthesis as a single piece with extensions through which anchoring sutures may pass and thus expose to the blood stream nothing but the Ivalon itself. Although this softness and pliability has definite advantages, it was soon learned during experiments on dogs, post-mortem hearts and dead beef hearts, that in order to stop the flow of fluid under approximately 120 mm. of mercury pressure through a defect it was necessary to have the size of the Ivalon approximately 25 per cent greater than the opening. Also, it was soon learned that such excessive bulk was objectionable because the mass of Ivalon above the line of cusp contact would tend to "bulge over" and thus obstruct the flow of blood from the atrium into the ventricle. Further experimentation using a simple type of pulse duplicator demonstrated that the insertion of a solid rod into the center of the soft Ivalon would maintain the peripheral pliability and moldability and still produce obstruction of a defect with a prosthesis of only slightly greater size (Fig. 1). This principal was applied clinically by placing a compressed Ivalon insert of appropriate size and shape into a slit in the body of the prosthesis.

Preparation of Prosthesis

The prosthesis is carved from a block of Ivalon about 2 x 4 x 18 cm. in size, using a sharp, long-bladed knife and scissors. It is cut so that it consists of 3 anchoring tails and a wedge-shaped body approximately 2 x 4 x 4 cm. in dimensions with the greatest cross section or base toward the ventricular chamber. In the early cases the base of the wedge was placed in the atrium with the apex in the ventricle. Later, however, the wedge was inverted in order to minimize the tendency to inflow obstruction (Fig. 2, A, B, C,). Two anchoring tails extend proximally from the apex or atrial aspect of the wedge and a single tail from the center of the base. Heavy No. 2 braided silk is then threaded through each atrial tail passing through the corresponding side of the body and out the ventricular tail. It is important to fix the heavy silk securely to the encasing Ivalon tails using two or three interrupted fine silk sutures to prevent the tails from tele-

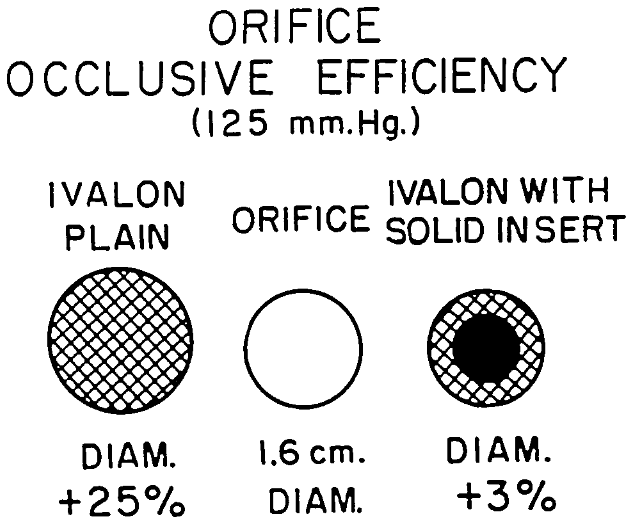

FIGURE 1: The flow of water under 125 mm. of mercury pressure through a circular valvular defect 1.6 cm. in diameter can be stopped by an Ivalon column of 25 per cent greater diameter. Using a solid rod insert one-half of the linear diameter of the Ivalon column, the same occlusive effect is obtained with an overall diameter increase of only 3 per cent.

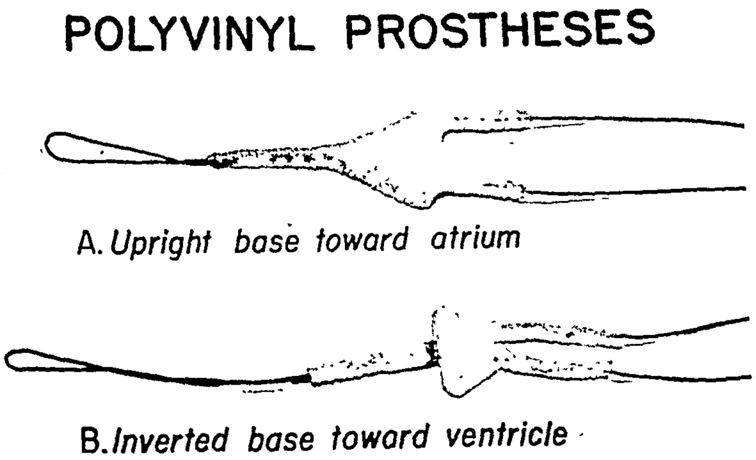
POLYVINYL PROSTHESES
A. Upright base toward atrium
B. Inverted base toward ventricle

FIGURE 2A

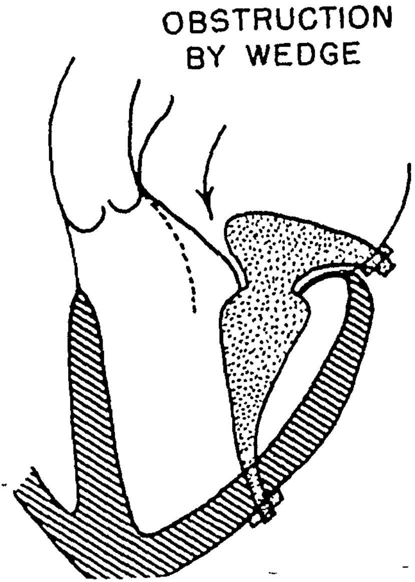

FIGURE 2B

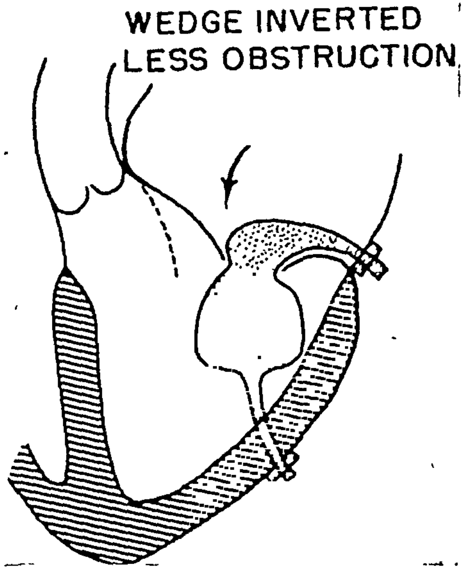

FIGURE 2C

Figure 2A: A) Model of original upright prosthesis with base of wedge toward atrium. B) Current model with apex and two anchoring tails toward atrium. Anchoring silk shown passing through prosthesis.—*Figure 2B:* Base of plain Ivalon wedge toward atrium showing tendency of soft Ivalon to "bulge" over line of closure producing ventricular inflow obstruction. *Figure 2C:* Wedge inverted to minimize obstruction.

scoping or bunching up on the heavy silk as the anchoring tails are pulled out through the walls of the heart. The tails should be about 5 mm. in diameter, which is large enough to tamponade the puncture wounds in the heart muscle and thus control bleeding. The roughly formed prosthesis is then washed well, preferably overnight in running water in a screened vessel. It is then autoclaved under water along with the instruments to be used for the case or it can be sterilized by boiling for 20 minutes. The compressed Ivalon, which is to be used for the firm insert, is prepared by packing long rods of well washed sponge into a glass test tube until it is reduced to approximately ¼ of its original volume, after which it is sterilized as above. After removal from the tube it will be found to be about the consistency of medium soft latex rubber. At the operating table the defect in the valve is examined and an appropriately shaped fragment of the compressed Ivalon, approximately ½ the linear dimensions of the body, is inserted into a slit in the prosthesis after which it is closed with fine buried sutures (Fig. 3). The prosthesis is then finally trimmed to a shape as near that of the orifice as possible and to a size 5 to 10 per cent larger than the insufficient opening. It is then soaked with penicillin solution and is ready for insertion.

Introduction of the Prosthesis

The heart is exposed through a long, routine posterolateral incision below the 6th rib, which is cut posteriorly (also 5th, if necessary). An umbilical tape is placed around the aorta just distal to the subclavian artery and passed through a broad based flexible tourniquet which will allow aortic compression during any manipulation which grossly obstructs the flow of blood across the mitral valve. We feel that this is important since it aids greatly in maintaining adequate central aortic, coronary and cerebral arterial pressure which otherwise would drop to dangerously low

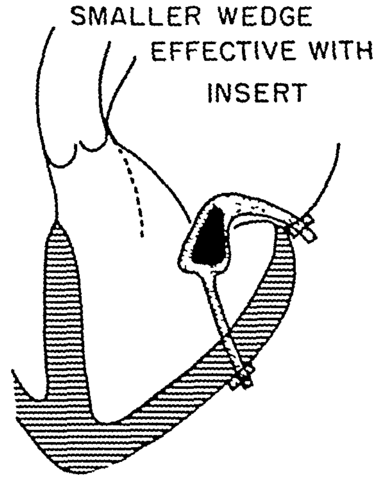

FIGURE 3

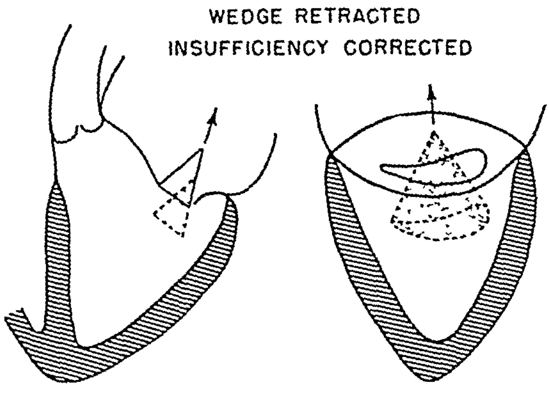

FIGURE 4

Figure 3: Insert of compressed Ivalon approximately 50 per cent of linear diameter of wedge increases occlusive efficiency and allows for decreased overall size of prosthesis.—*Figure 4:* Diagram showing adjustability of prosthesis after insertion into the heart by advancement or retraction.

levels.[22] The pericardium is incised posterior to the phrenic nerve to expose the entire lateral surface of the heart, including the atrioventricular junction to the region of the termination of the coronary sinus. Heavy silk sutures are placed in the pericardium to allow strong traction which rotates the heart outward to provide adequate exposure. A purse string suture is placed around the base of the auricular appendage, using closely placed stitches to minimize the likelihood of tearing out which might result from repeated manipulations through the atrial incision and the ends controlled with a flexible tourniquet. The atrium and the valve are then explored, paying particular attention to the flexibility of the major leaflet, since if adequate mobility is not present or cannot be attained through generous commissurotomy, both anterolaterally and posteromedially, then the lesion probably is not amenable to correction by the use of any fixed or relatively fixed prosthesis. To obstruct such a defect in the absence of good mobility of the major leaflet would simply convert insufficiency into stenosis. One can be more liberal with the commissurotomy using whatever technique is necessary, inasmuch as the prosthesis can be shaped to correct any increased leakage, particularly if it occurs toward the mural leaflet. Even if some disruption of the chordae tendineae of this cusp occurs, the prosthesis is apt to correct it, since mechanically it functions somewhat like a large chordal structure if the atrial tail is placed in the region of the chordal damage. Appropriate sites of exit for the ventricular and atrial tails are then chosen to center the prosthesis opposite the point of maximal leakage. The site in the ventricle should be approximately ½ the distance from the apex to the atrioventricular junction and as far away from the major coronary branches as possible. The atrial exit points are chosen just proximal to the vessels in the atrioventricular junction and should be situated so that the angle made by the two tails is very near a straight line. It is important to place the posterior tail very far back—farther than one would anticipate—and near the termination of the coronary sinus, so that the wedge can be pulled into the posteromedial commissure where the maximal leak is apt to be present. A malleable suture passer with an eye in its distal end is then threaded with the heavy anchoring silk emerging from the ventricular tail, and this is passed through the atrium along the ungloved right index finger down into the ventricular chamber, using care not to entangle the papillary muscle or chordae tendineae, and out the chosen ventricular site. (An alternative method is to pass the instrument in a retrograde fashion, thread it and pull it back out the ventricular wall.) Traction on the ventricular tail then advances the body of the wedge into the atrium, with or without removing the finger, and downward into the ventricle. Great care must be used to pull in the proper axis in order to avoid tearing the friable ventricular muscle. Bleeding from the ventricular wound is usually controlled by the bulk of the tail, although a round button of Ivalon is usually pulled over it and against the surface of the myocardium. The process is repeated with each atrial tail, using extreme care to pull in the proper axis to avoid laceration of the thin atrial wall. However, if this should occur, hemorrhage can be controlled readily by placing the intra-atrial finger against the tear while sutures are placed externally. The position of the body of the prosthesis is then adjusted by advancement or retraction to increase or decrease the cross sectional area of the wedge lying between the leaflets (Fig. 4). The two atrial tails are then adjusted to pull the wedge toward one commissure or the other in order to bring about maximal obliteration of the regurgitant jet. After the best possible control is attained the tails and the buttons are sutured to the myocardium using several stitches, after which the redundant ends of the tails are excised. It is important to use care in placing these sutures, since the ventricular contractions postoperatively may have a tendency to slide the buttons away from the ventricle with resultant hemorrhage, especially after pericardial roughening has occurred. The chest cavity is then irrigated well with saline solution and closed in a routine manner.

Results

I. Tolerance of Operation:

Dogs tolerated the technical procedure of introducing the prostheses very well, and rather surprisingly, the five patients—four of whom were Class IV patients with low reserves—had virtually no more difficulty with hypotension, arrhythmias or other problems than one would expect from a simple commissurotomy in such patients. Obviously, blood loss was somewhat greater than for a simpler procedure but with adequate replacement no difficulty was encountered. The tolerance of our first patient was particularly notable, since she was very close to the state of uncontrollable decompensation with massive ascites and hydrothorax, which responded very slowly to preoperative medical management (Fig. 5). On two occasions her surgery had to be cancelled because of the development of tachycardia with a rate of around 180 followed by pulmonary congestion. In spite of this, she was scheduled a third time and went through the procedure with no significant difficulty, other than a spell of tachycardia lasting for about 2 minutes before responding to neostigmine.

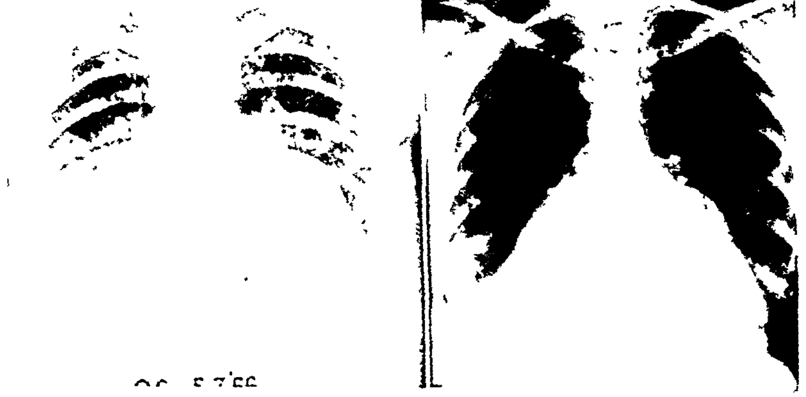

FIGURE 5: Chest roentgenograms showing type of Class IV patient selected for surgery before and after intensive medical preparation.

II. Degree of Correction:

In animals attempts were made to estimate the efficiency of the prostheses in correcting regurgitation produced by biting out a semicircular piece of the mural cusp. However, after several experiments we became convinced that the pathology of such insufficiency was not comparable to that found in patients and, therefore, the effectiveness of the method could not be judged. Further experiments to settle this point were therefore abandoned. Our initial plan, to quantitate the degree of correction of insuffciency, was to take simultaneous left ventricular and left atrial pressures before and after repair, in addition to estimating the volume by palpation, which admittedly is a gross determination. However, in animal experiments as well as clinical cases, the pressure measurements added significantly to the operative time and also gave unexpected conflicting results which led to efforts to explain them. On one occasion, when by palpation, the volume of the residual jet seemed to be small, the intra-atrial pressure, as recorded, was found to be unexpectedly high. We therefore set up a simple experiment measuring the pressures in a fluid-filled container into which a circular jet of water was flowing at a pressure corresponding to approximately 120 mm. of mercury. Using a beveled needle to control the position accurately, great variation in pressure readings was found depending on the relationship of the needle tip to the jet and also on the relationship of the bevel to the jet (Fig. 6).

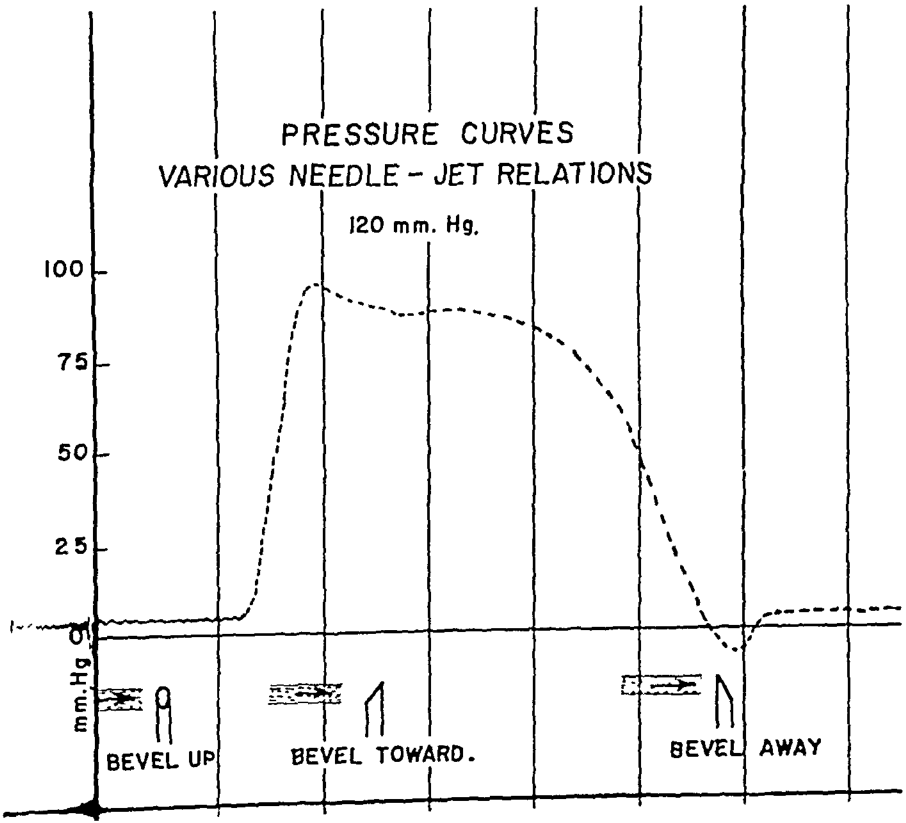

FIGURE 6: Chart showing marked variation in pressures in a chamber depending on the relationship of needle tip to the entering jet of fluid.

The pressures varied from a maximum of near 100 mm. of mercury to a negative reading of approximately minus 4 mm. of mercury. This wide variation, which was brought about by only one of the many variables, i.e., rotation of the needle bevel, caused us to doubt the validity of such pressure readings until other factors are better controlled. In 3 patients it was estimated that approximately 80 per cent of the regurgitant jet had been obliterated and 75 per cent in a fourth, even though simple, uncompressed Ivalon was used. In the fifth patient approximately 85 per cent correction was attained using a smaller prosthesis containing a compressed insert. In two instances, the prosthesis definitely was not pulled sufficiently far into the posteromedial commissure, so that considerable leakage persisted in this area (Fig. 7). Definite evidence of stenosis has not developed in any case to date, although in one instance we are concerned about this possibility. Here a prosthesis was used in the face of a relatively small orifice and somewhat questionable leaflet mobility after the cross-polar plication method failed when the internal suture pulled out. A mitral stenotic murmur is present, but as yet no objective or subjective evidence of stenosis has appeared.

III. Hemorrhagic Diathesis:

Fortunately, an outspoken picture of a true hemorrhagic state has not been encountered, as yet. One patient died postoperatively primarily from hemorrhage, although the site, most likely, was the ventricular wound which was unusually large due to technical difficulties in pulling the prosthesis through the wall. This patient had a congenital absence of the pericardium which, throughout the years, allowed her progressively enlarging heart to shift backward into the posterior gutter. In the absence of the pericardial sac there was nothing which could be grasped

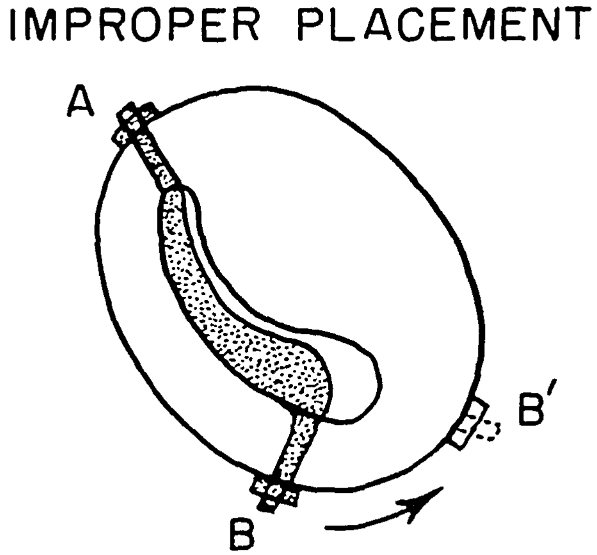

FIGURE 7: Prosthesis improperly placed being centered too far anteriorly, thus allowing persistent posterior leak. Shift of exit point of atrial tail, B to B^1, would correct this difficulty.

safely in order to rotate the heart around into a position of adequate surgical accessibility. The bleeding, which was evident before closure, seemed to be very well controlled but sutures were not placed around the periphery of the Ivalon button, due to the proximity of the descending branch of the left coronary artery. It seems likely that motion postoperatively caused recurrence of the bleeding, and this impression was substantiated by the escape of fluid from this tract when the ventricle was distended post-mortem. Platelet counts, clot retraction, bleeding and clotting time determinations have not been notably altered in the postoperative period.

IV. Hemolytic Reaction:

The development of anemia with an increase in serum bilirubin, after the effects of bleeding related to surgery were passed, occurred in one patient to a moderate degree, thus requiring four 500 cc. blood transfusions during the first five days after operation. A second patient, who died postoperatively, developed definite evidence of hemolysis of considerable degree along with an unexplainable hyperpnea up to 70 per minute immediately on awakening from the anesthetic and persisting for 48 hours. Check-up examination on the transfused blood excluded a hemolytic transfusion reaction beyond reasonable doubt. The discovery at autopsy of pigment gall stones and splenomegaly in this 18 year old youth suggested a pre-existing hemolytic defect, although all pre- and postoperative studies failed to establish its nature. Three survivors up to 5 months postoperatively have not become anemic. How important hemolysis may prove to be cannot be stated in view of our present knowledge.

V. Thrombo-embolic Phenomena:

To date, signs or symptoms suggesting thrombo-embolic complications have not been recognized.

VI. Other Complications:

No evidence of postoperative infection or of other significant complications has been encountered.

Discussion

The technical maneuvers involved in the method described appear to be tolerated relatively well, even in patients who have advanced heart disease with a low cardiac reserve. Correction of mitral insufficiency by taking advantage of the principle of progressive advancement of a wedge-shaped prosthesis through the mitral orifice seems to be simpler technically and more controllable than most other methods. The prosthesis described, which has adequate firmness due to the insertion of a centrally placed fragment of compressed Ivalon plus peripheral soft moldability, appears to possess physical properties inherently capable of obliterating mitral insufficiency to a greater degree than is possible with other materials due to its ability to conform to the irregular, firm, cusp edges. The extremely low incidence of thrombo-embolic phenomena in animals and the absence of such complications in the few patients treated to date is encouraging, but by no means excludes the possibility of such complications. The frequency and seriousness of hemorrhagic and hemolytic reactions cannot be estimated at the present time. Neither can the possibility of late stenosis be excluded. Because of these considerations, the indiscriminate and widespread application of this method is certainly not advisable until some of the above questions are answered by further observations and further passage of time.

SUMMARY AND CONCLUSIONS

1. A method for correcting mitral insufficiency using a transvalvular polyvinyl formalinized (Ivalon) sponge has been described.

2. Experience with placement of Ivalon in the region of the mitral valve in experimental animals and in a few patients indicates that the incidence of serious complications is low. This may well be due to the ingrowth of vascular fibrous tissue and surface "endothelialization." The characteristics of the implanted Ivalon become somewhat similar to living tissue.

3. The technique, as described, appears to be well tolerated and the degree of correction of the insufficiency can be controlled within reason after the prosthesis has been placed within the heart.

4. Experience with the method is so limited that the operative mortality rate, the incidence of complications and the results cannot be estimated at the present time.

5. The early results seem to be favorable enough to justify further limited clinical application but widespread clinical use is inadvisable.

RESUMEN Y CONCLUSIONES

1. Se describe un método para corregir la insuficiencia mitral usando una esponja transvalvular de polivinilo formalizado (Ivalon).

2. La experiencia con la colocación del Ivalón en la región de la válvula mitral en los animales de experiencia en algunos enfermos indica que la incidencia de complicaciones serias, es baja. Esto bien puede deberse a la penetración de tejido vascular fibroso neoformado y en la creación de una superficie de "endoepitelización."

Las características del Ivalón implantado se hacen algo similares al tejido vivo.

3. La técnica como de describe, parece conducir a una buena tolerancia y el grado de corección de la insuficiencia puede controlarse razonablemente después de que prótesis se ha colocado en el interior del corazón.

4. La experiencia en el método es tan limitada que la mortalidad operatoria, la incidencia de las complicaciones y los resultados no pueden estimarse aún al presente.

5. Los resultados tempranos parecen suficientemente favorables para justificar su empleo ulterior en aplicación clínica limitada pero el uso extenso clínicamente no es aconsejable.

RESUME

1. L'auteur décrit un procédé pour corriger l'insuffisance mitrale, en utilisant une éponge transvalvulaire en polyvinyle formolée (Ivalon).

2. L'expérience avec la mise en place de l'éponge d'Ivalon dans la région de la valvule mitrale chez les animaux et chez un petit nombre de malades montre que la fréquence des complications graves est faible. Ceci pourrait bien être dû à l'accroissement de tissu vasculaire fibreux et à une "endothélialisation" de surface. Les caractères de l'Ivalon greffé deviennent en quelque sorte semblables à ceux du tissu vivant.

3. La technique, selon la description qui en a été donnée, semble être bien tolérée, et le degré de la correction de l'insuffisance peut être contrôlé rationellement après que la prothèse a été placée dans le coeur.

4. L'expérience de cette méthode est encore si limitée que le taux de mortalité opératoire, la fréquence des complications, et les résultats ne peuvent être estimés pour le moment.

5. Les résultats précoces semblent être suffisamment favorables pour justifier des essais cliniques ultérieurs limités, mais l'emploi étendu en pathologie médicale ne doit pas encore être conseillé.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNG

1. Es wurde eine Methode beschrieben zur Korrektur der Mitralinsuffizienz unter Verwendung eines mit Formalin (Ivalon) behandelten transvalvulären Polyvinylschwammes.

2. Erfahrungen mit der Unterbringung von Ivalon in der Gegend der Mitralklappe bei Versuchstieren und bei einigen wenigen Patienten ergibt, dass das Auftreten von ernsthaften Komplikationen selten ist. Dies kann sehr wohl die Folge sein des Einwachsens von gefässhaltigem Bindegewebe und einer oberflächlichen "Endothelialisierung." Die Eigenschaften des implantierten Ivalons werden bis uz einem gewissen Grade denen des lebenden Gewebes ähnlich.

3. Die Technik, wie sie beschrieben wird, scheint gut vertragen zu werden, und das Ausmass der Korrektur der Insuffizienz kann bis zu einem gewissen Grade beherscht werden, nachdem die Prothese im Herzen angebracht ist.

4. Die Erfahrung mit dieser Methode ist so begrenzt, dass die operative Sterblichkeit, die Häufigkeit von Komplikationen und die Ergebnisse im Augenblick noch nicht abgeschätzt werden können.

5. Die Anfangserfolge scheinen günstig genug zu sein, um in begrenztem Rahmen weitere klinische Anwendung zu rechtfertigen, jedoch ist allgemeine Benutzung nicht ratsam.

REFERENCES

1 Murray, G., Wilkinson, F. R. and McKenzie, R.: "Reconstruction of the Valves of the Heart," *Canad. M.A.J.*, 38:317, 1938.
2 Templeton, J. Y. III and Gibbon, J. H. Jr.: "Experimental Reconstruction of Cardiac Valves by Venous and Pericardial Grafts," *Ann. of Surg.*, 139:161, 1949.
3 Murray, G.: "Treatment of Mitral Valve Stenosis by Resection and Replacement of Valve Under Direct Vision," *Arch. Surg.*, 61:903, 1950.

4 Bailey, C. P., O'Neill, T. J. E., Glover, R. P., Jamison, W. L. and Redondo-Ramirez, H. P.: "Surgical Repair of Mitral Insufficiency," *Diseases of the Chest*, 19:125, 1951.

5 Bailey, C. P., Jamison, W. L., Bakst, A. E., Bolton, H. E., Nichols, H. T. and Gemeinhardt, W., M.Sc.: "Surgical Correction of Mitral Insufficiency by Use of Pericardial Grafts," *J. Thor. Surg.*, 28:551, 1954.

6 Harken, D. W., Black, H., Ellis, L. B. and Dexter, L.: "The Surgical Correction of Mitral Insufficiency," *J. Thor. Surg.*, 28:604, 1954.

7 Johns, Thos. N. P. and Blalock, A.: "Mitral Insufficiency: The Experimental Use of a Mobile Polyvinyl Prosthesis," *Ann. of Surg.*, 140:335, 1954.

8 Davila, J. C., Mattson, W. W. Jr., O'Neill, T. J. E. and Glover, R. P.: "A Method for the Surgical Correction of Mitral Insufficiency," *Surg., Gynec. & Obst.*, 98:407, 1954.

9 Glenn, Wm. W. L. and Turk, L. N. III: "The Surgical Treatment of Mitral Insufficiency: The Fate of a Vascularized Transchamber Graft," *Ann. of Surg.*, 141:510, 1955.

10 Bailey, C. P.: *Surgery of the Heart*, Lea and Febiger, 1955.

11 Harken, D. E.: *The Surgical Treatment of Mitral Insufficiency, Henry Ford Hospital International Symposium on Cardiovascular Surgery*, W. B. Saunders Co., 1955, p. 212.

12 Bailey, C. P., Bolton, H. E., Jamison, W. L., Nichols, H. T. and Likoff, W.: *Methods of Surgical Treatment for Valvular Insufficiency of the Heart, Henry Ford Hospital International Symposium on Cardiovascular Surgery*, W. B. Saunders Co., 1955, p. 222.

13 Glenn, Wm. W. L., Gentsch, T. O. L., Hume, M. and Guilfoil, P. H.: "The Surgical Treatment of Mitral Insufficiency with Particular Reference to the Application of a Vertically Suspended Graft," *Surgery*, 40:64, 1956.

14 Glover, R. P. and Davila, J. C.: "The Treatment of Mitral Insufficiency by the Purse String Technique," *J. Thor. Surg.*, 33:75, 1957.

15 Nichols, H. T.: "Mitral Insufficiency: Treatment by Polar Cross-Fusion of the Mitral Annulus Fibrosus," *J. Thor. Surg.*, 33:102, 1957.

16 Kernan, M. C., Newman, M. M., Levowitz, B. S., Stuckey, J. H. and Dennis, C., with the technical assistance of Alva Riddick and Herbert Lauritzen: "A Prosthesis to Replace the Mitral Valve," *J. Thor. Surg.*, 33:698, 1957.

17 Harken, D. E.: Personal Communication, April 3, 1957.

18 Bailey, C. P.: Personal Communication, March 1957.

19 Stohlman, F. Jr., Sarnoff, S. J., Case, R. B. and Ness, A. T.: "Hemolytic Syndrome Following Insertion of Lucite Ball Valve Prosthesis into Cardiovascular System," *Circulation*, 13:586, 1956.

20 Grindlay, J. H. and Waugh, J. M.: "Plastic Sponge Which Acts as a Framework for Living Tissue: Experimental Studies and Preliminary Report of Use to Reinforce Abdominal Aneurysms," *A.M.A. Arch. Surg.*, 63:288, 1951.

21 Mortensen, JD and Grindlay, J. H.: "Molded Seamless Tubes of Polyvinyl Formalinized Sponge," *A.M.A. Arch. Surg.*, 72:871, 1956.

22 Rumel, W. R., Cutler, P. R. and Mortensen, JD: "Practical Problems in Surgical Treatment of Mitral Stenosis," *J. Int. Coll. Surg.*, 157:170, 1956.

The Occurrence of Arrhythmias in Acute Myocardial Infarctions

C. CLIFFORD JOHNSON, M.D. and PAUL F. MINER, M.D., F.C.C.P.
Boise, Idaho

Introduction

Numerous statistical studies have been made on arrhythmias occurring in persons with acute myocardial infarctions. Most investigations have been made and reported from teaching hospitals in large medical centers. For this reason such studies have usually been carried out on patients of a similar social and economic status, not necessarily a true cross section of the general population. We believe it worthwhile to undertake a similar type of study of all patients treated for acute myocardial infarctions who were seen in two community general hospitals during a five year period (1950-1954). Thus our report attempts to evaluate such studies made on a group representative of all economic and social spheres.

Method of Study

Only those with clinical evidence of acute myocardial infarction such as pain, fever, leukocytosis, and elevated sedimentation rate were included in this study. All of them had definite electrocardiographic evidence of acute infarctions. A total of 187 patients was selected as fulfilling these criteria. They were studied from a standpoint of occurrence as arrhythmias in relation to location of the infarction, hypertension, sex, age, and mortality and other complicating factors, such as cardiac failure and shock.

Findings

Incidence, Age, and Sex: The percentage of arrhythmias occurring, excluding extrasystoles and bundle branch block, was 16.5 per cent (31 of 187 cases). This value compares with those of Mintz and Katz[1] who found 16.4 per cent in a study of 572 cases. Master et al[2] found 14 per cent in a review of 300 cases. Totibouet[3] in France found 8 per cent in a study of 420 cases while Griffith[4] reported an incidence of 17 per cent in myocardial infarction from the Los Angeles County Hospital.

There was an increased incidence of arrhythmias in the older age groups. Among the group of patients with arrhythmias there were 24 (77.4 per cent) over 60 years of age and 7 (22.6 per cent) under 60 years. In all cases of infarctions there were 111 (59.4 per cent) over 60 years of age and 76 (40.6 per cent) of 187 patients under 60 years of age. There was not only an increased incidence of arrhythmias but also an increased mortality in the older age groups. Twenty of 26 deaths with anterior infarction were in patients over 70 years of age and 10 of 18 deaths with posterior infarctions were in those over 70 years old (Table I).

From the Department of Medicine of St. Luke's Hospital and St. Alphonsus Hospital.

From the total number of cases studied, there were 89 (47.3 per cent) with an anterior and 98 (52.7 per cent) with a posterior infarction. Although the total incidence of anterior and posterior infarctions was nearly the same, the sex incidence was considerable different. Men constituted 75.9 per cent of all cases studied and women 24.1 per cent. The men had an incidence of 63 (70.5 per cent) of the 89 cases of anterior infarction while the women had 26 (29.5 per cent). Of those with posterior infarction 79 (80.6 per cent) were in men and 19 (19.4 per cent) were in women. This would suggest that a proportionately higher incidence of posterior infarction occurred in men. In this series 81 per cent of the arrhythmias occurred in men and 19 per cent in women. This is nearly the same proportion as infarction occurred in the two sexes, indicating that the arrhythmias appeared with similar frequency in both sexes. Master[2] reported that arrhythmias were more prone to develop in women than in men while Mintz and Katz[1] stated that the incidence was about the same in both sexes. In our series of arrhythmias there was an incidence of 10 cases (10.6 per cent) with anterior infarction and 21 (22.4 per cent) with posterior infarction (Table I, II and III).

Types of Arrhythmias: The most common type of arrhythmias was auricular fibrillation. It occurred in 16 (8.7 per cent) of a total of 187 patients. There was an incidence of 8 (9.1 per cent) of 89 with anterior infarction and 8 (8.2 per cent) of 98 with posterior infarction.

TABLE I

AGE DISTRIBUTION OF ALL CASES WITH MYOCARDIAL INFARCTION

Age in Years	Number of Cases
31 - 40	4
41 - 50	18
51 - 60	54
61 - 70	61
71 - 80	43
81 - 90	7
TOTAL	187

AGE DISTRIBUTION OF CASES WITH ARRHYTHMIAS

Age in Years	Number of Cases
41 - 50	3
51 - 60	4
61 - 70	12
71 - 80	10
81 - 88	2
TOTAL	31

Atrioventricular block was noted in 11 (5.9 per cent). Of these, only one occurred with anterior infarction. This case was associated with a first degree block. Ten (10.1 per cent) of 98 patients with posterior infarction had heart block, in seven of whom it was complete. Because the right coronary artery supplies the atrioventricular node in 92 per cent of patients,[5] nearly all cases of atrioventricular block are associated with posterior artery occlusions.

Ventricular tachycardia was recorded in only one instance and this was a patient with posterior infarction. He also developed a nodal tachycardia during his stay in the hospital.

One case of auricular flutter was noted. In various series in the literature the incidence of flutter has been reported from 1 per cent to 4.3 per cent. Master[2] reported 1 per cent in 300 cases and Mintz and Katz[1] found 4.3 per cent in 524 patients with acute myocardial infarctions.

There was no case of auricular tachycardia identified in our series, however, there were two with nodal rhythms. These types of arrhythmias have been reported to be uncommonly associated with acute myocardial infarctions. Bellet[6] stated that supraventricular tachycardia was seen in only 5 of 1,247 cases of myocardial infarctions. In a series of 872 patients reviewed by Askey[7] only eight had supraventricular tachycardia.

Complicating Factors: Hypertension (blood pressure over 160/90) was found in 56 (29.9 per cent) of the patients. Of these there was an incidence of 31.9 per cent with an anterior infarction and 29 per cent with posterior infarction. Another complicating factor, appearing with almost equal frequency in both anterior and posterior infarction, was shock, with a total incidence of 14.5 per cent. There was 13.5 per cent in anterior infarction and 15.5 per cent in posterior infarction. Heart failure occurred in 29 (15.5 per cent). Of those with heart failure 18 (20.2 per cent) were in the group with anterior infarction and 11 (11.2 per cent) in the posterior infarctions cases (Table IV).

Mortality: The over-all mortality was 23.5 per cent in 187 patients. The mortality of those with arrhythmias was 29 per cent (9 of 31 cases) while the rate in those without arrhythmias was 22.4 per cent (35 of 156 cases). The rate in all patients with anterior infarctions was 29.2 per cent and in posterior infarction it was 18.3 per cent. There was a mortality of 20.3 per cent among the men and 33.3 per cent among the women. Anterior infarction caused deaths more frequently in men than did posterior—26.8 per cent to 15.6 per cent, respectively. Mortality was essen-

TABLE II
PERCENTAGE OF PATIENTS WITH ANTERIOR AND POSTERIOR MYOCARDIAL INFARCTION

	Anterior	Posterior	Total
Males	70.5	80.6	75.9
Females	29.5	19.4	24.1

tially the same in women with either anterior or posterior infarctions—34.5 per cent to 31.5 per cent. Patients having heart failure and myocardial infarction had a higher mortality (49 per cent). In those in whom shock occurred, mortality was 52 per cent, and in those with auricular fibrillation it was 31 per cent. Two of the seven with complete heart block died (Table V).

Discussion

Arrhythmias in acute myocardial infarction are known to increase the mortality. Rosenbaum and Levine[9] found the mortality to be increased from 27 per cent for those without arrhythmias to 42 per cent for those with arrhythmias. Our mortality for 31 with arrhythmias was 29 per cent compared to 22.4 per cent in cases without arrhythmias. These findings seem to be in agreement with others.[2, 10] Hence it would appear that the prompt and accurate diagnosis and treatment of arrhythmias in myocardial infarction might be life-saving.

Auricular fibrillation was the most common arrhythmia in our series. This type had a mortality rate of 31 per cent which was greater than our over-all mortality of 23.5 per cent. Rosenbaum and Levine[9] thought the occurrence of auricular fibrillation after myocardial infarction did not appreciably alter the prognosis. Any increase in mortality has been ascribed to heart failure or shock rather than to the arrhythmia. However, Askey[11] felt the prognosis was worse if the arrhythmia persisted. Also he stated that the longer the fibrillation persisted, the greater became the hazard of embolism. Billings[12] found that the presence of auricular fibrillation at the time of the acute attack increased the mortality during the first 30 days.

A high incidence of auricular fibrillation has been reported to be associated with lateral wall infarction by Wood, Wolferth and Bellet.[13] Cushing[14] found a high incidence in solitary atrial infarctions. He observed abnormalities of the auricular mechanism of the electrocardiogram in 74 per cent of the cases of atrial infarction. Others[1, 9, 12] noted no correlation between auricular fibrillation and the location of the infarct. In our series

TABLE III

PERCENTAGE OF VARIOUS ARRHYTHMIAS OCCURRING IN ANTERIOR AND POSTERIOR INFARCTION

	Anterior	Posterior	Total
Arrhythmias—Excluding extrasystoles and B.B.B.	10.6	22.4	16.5
Auricular Fibrillation	9.1	8.2	8.7
Atrioventricular Block	1.1	10.1	5.9
Ventricular Tachycardia	0	1.0	0.5
Nodal Tachycardia	0	2.0	1.4
Auricular Flutter	0	1.0	0.54

there was an equal number of patients with anterior and posterior infarctions who were found to have auricular fibrillation.

Heart block is another type of arrhythmia commonly associated with myocardial infarctions. Goldman[15] stated that it is generally agreed that complete heart block following myocardial infarction is practically always associated with posterior infarction. Fifty-nine of 60 cases of heart block reported by Master[16] had posterior infarctions. All of our cases of complete heart block were associated with posterior infarctions. As previously noted, the one case occurring with anterior infarction had first degree block. Gross[5] pointed out that the blood supply to the auriculoventricular node is usually from the right coronary artery and this is the likely reason of heart block being associated with posterior infarction. Master[16] stated that the atrioventricular node is very sensitive to ischemia, so any cause of anoxia can produce heart block.

Mortality is distinctly higher when heart block occurs. Mintz and Katz[1] reported 100 per cent, but Bellet[6] found recoveries were not so rare. In our series two of seven cases with complete heart block, one of first degree block, and the one with sino-auricular block died. Rosenbaum and Levine[9] reported that once heart block develops in association with acute myocardial infarction, and the patient survives, complete recovery from the block or a lesser degree of block tends to be the ultimate outcome. Graybiel and White[17] found 10 per cent of patients with complete heart block had had myocardial infarctions.

In our series other types of arrhythmias were uncommon. Only one case of auricular flutter and one of ventricular tachycardia were noted. However, these types could have occurred more commonly than were diagnosed. This might have been true in terminal states where rapid cardiac rates were noted either in the physicians' or nurses' notes but were not further identified.

Ventricular tachycardia occurs most often in association with organic heart disease.[18] Cooke and White[19] in reviewing the records of 25,000 patients at Massachusetts General Hospital found 27 instances of ventricular tachycardia. Twenty-two of these had coronary heart disease. They further state that considering the large number seen with coronary heart disease, there were few instances of ventricular tachycardia and that coronary heart disease by itself must play only a minor role in initiating this arrhythmia. Infarction with its various disturbances in the muscle and circulation should provide numerous occasions for the escape of the ectopic

TABLE IV

PERCENTAGE OF COMPLICATIONS OF MYOCARDIAL INFARCTION

	Anterior	Posterior	Total
Hypertension	31.9	29.0	29.9
Shock	13.5	15.5	14.5
Heart Failure	20.2	11.2	15.5

rhythmic centers; however, the incidence is extremely small. Digitalis has been known to precipitate ventricular tachycardia as have other substances.[18,20] Only two of Cooke and White's 22 patients with ventricular tachycardia survived longer than two years after the attack.

Ambrust and Levine[20] reviewed 107 cases of ventricular tachycardia and found that 79 (74 per cent) had coronary heart disease. Forty-four of the 79 had myocardial infarctions. The duration of the attacks may be a few seconds to days—one having been reported to have lasted 71 days.[20] Sixty-four of the 79 cases reported by Ambrust and Levine were dead within one month.

Supraventricular tachycardias are much more frequently associated with non-organic heart disease.[18] Master,[3] however, reported five supraventricular tachycardia out of 300 cases of myocardial infarctions. Only one of the 300 had ventricular tachycardia. Mintz and Katz[1] reported an incidence of 3.2 per cent of supraventricular tachycardias in their patients with myocardial infarctions while 5.3 per cent had ventricular tachycardias. Supraventricular tachycardias are usually not serious except in the presence of myocardial infarction and then they may be fatal unless quickly stopped. Sinus tachycardias rarely exceed a rate of 140 but the persistence of such a rapid rate with myocardial infarctions carries a poor prognosis. Billings et al.[12] noted that mortality in myocardial infarction was much higher in those with pulse rate over 100.

Arrhythmias were more common in those with posterior infarctions in our series. The incidence was 22.4 per cent compared to 10.6 per cent in anterior infarctions. Mortality was higher in those occurring with anterior infarctions which may have been due to the fact that the percentage with heart failure was twice as high in anterior as in posterior infarction. Mortality in those with heart failure was 55 per cent with anterior infarctions and 45 per cent with those with posterior lesions.

TABLE V

PERCENTAGE OF MORTALITY FROM ANTERIOR AND POSTERIOR INFARCTION AND COMPARISON WITH ASSOCIATED COMPLICATING FACTORS AND SEX RELATIONSHIP

	Anterior	Posterior	Total
Deaths— with Heart Failure	55.0	45.5	49.0
Deaths— with Shock	58.0	53.0	52.0
Deaths— with Auricular Fibrillation	12.5	50.0	31.0
Deaths— with Heart Block	100.0	30.0	36.5
Deaths—Males	26.8	15.6	20.3
Deaths—Females	34.5	31.5	33.3
Mortality of all Cases	29.2	18.3	23.5

The exact mechanisms of arrhythmias remain unknown. However, the two factors principally involved in auricular fibrillation are increased parasympathetic stimulation of the vagus and anoxia of the myocardium. Of these factors anoxia would seem the more important in myocardial infarctions. Schlichter[21] observed the development of auricular fibrillation in a case of anemia and its disappearance after blood transfusion. According to Luisada[22] the most common cause of infarction is slow, gradual occlusion of an arteriosclerotic vessel by the concentric proliferation of the intima. Anoxia of the myocardium is the result. The common association of atrial infarction[14] with supraventricular arrhythmias would only serve to support the theory that anoxia is a likely etiologic factor. Since arrhythmias usually do not begin until several hours after infarction, Harris[23] believed that possible sympatho-adrenal substances liberated during necrosis of the muscle act as excitatory factors on the vagus to produce auricular fibrillation.

The treatment of these arrhythmias has been well covered in the literature. The cases studied were attended by various staff members of the two hospitals in which our study was made. Hence no attempt is made to evaluate the treatment in this study.

We feel that the dangers of the use of digitalis in patients with acute myocardial infarctions have been overemphasized. We agree with Askey[24] that quinidine should be given with digitalis, especially when premature beats appear. The fear of the production of ventricular tachycardia has deterred many physicians from using digitalis in acute infarctions when complicated by heart failure or auricular fibrillation. Gilson and Schemm[25] administered digitalis to patients with heart failure and ventricular tachycardia and found that the tachycardia disappeared and the heart failure was controlled. The authors believe that both digitalis and quinidine are contraindicated in the presence of complete heart block.

SUMMARY

1. Arrhythmias, excluding extrasystoles and bundle branch block, were found to be present in 16.5 per cent (31 of 187 cases) of acute myocardial infarctions reviewed in a study from two community general hospitals.

2. The over-all mortality of acute myocardial infarctions was 23.5 per cent and was higher among those with other complicating factors, such as heart failure or shock. Mortality of the patients with arrhythmias was 29.2 per cent (9 of 31) while the mortality in patients without arrhythmias was 22.4 per cent.

3. The relationship of the incidence of various types of arrhythmias to sex, age, site of infarctions and other complicating factors, such as heart failure and shock, has been discussed.

RESUMEN

1. En 16.5 por ciento de los infartos agudos del miocardio, se encontraron arritmias, excluyendo extrasístoles y bloqueo de ramas, según un estudio realizado en dos hospitales generales públicos.

2. La mortalidad global de los infartos agudos del miocardio fué 23.5 por ciento y fué más alta entre los que tenían otros factores complicantes tales como insuficiencia cardiaca o schock. La mortalidad entre los enfermos con arritmias fué 29.2 por ciento (nueve entre 21) en tanto que la mortalidad en enfermos sin arritmias fué de 22.4 por ciento.

3. Se ha discutido la relación de la incidencia de varios tipos de arritmias al sexo, edad, sitio del infarto y otros factores complicantes tales como insuficiencia cardiaca y schock.

RESUME

1. Mis à part les extrasystoles et le bloc de branches, l'auteur a constaté des arythmies dans 16,5% des cas (31 sur 187) d'infarctus aigus du myocarde, recueillis dans deux hôpitaux généraux publics.

2. La mortalité moyenne des infarctus aigus du myocarde a été de 23,5% et se montra plus élevée chez les malades atteints de complications, telles qu'insuffisance cardiaque ou shock. La mortalité des malades atteints d'arythmies fut de 29,2% tandis que la mortalité des malades sans arythmies fut de 22,4%.

3. L'auteur a discuté les rapports entre les différents types d'arythmies et le sexe, l'âge, le siège de l'infarctus et les autres facteurs de complications, tels que l'insuffisance cardiaque et le shock.

ZUSAMMENFASSUNG

1. Arrhythmien ausser Extrasystolen und Herzblock wurden vorgefunden in 16,5% (31 von 187 Fällen) von akutem Myocard-Infarkt, die in einer Untersuchungsreihe aus 2 städtischen allgemeinen Krankenhäusern einer Durchsicht unterzogen wurden.

2. Die Gesamtsterblichkeit des akuten Myocard-Infarktes betrug 23,5% und lag höher bei solchen mit anderen komplizierenden Faktoren wie Herzinsuffizienz oder Schock. Die Sterblichkeit der Patienten mit Arrhythmie betrug 29,2% (§ von 31) während die Mortalität bei Patienten ohne Arrhythmie bei 22,4% lag.

3. Besprechung der Beziehungen des Vorkommens verschiedener Typen von Arrhythmien zu Geschlecht, Alter, Lage eds Infarktes und anderen komplizierenden Faktoren so wie Herzinsuffizienzbund Schock.

REFERENCES

1 Mintz, S. S. and Katz, L. N.: "Recent Myocardial Infarction; and Analysis of Five Hundred and Seventy-Two Cases," *Arch. Int. Med.*, 80:205, 1047.

2 Master, A. M., Dack, S. and Jaffe, H. L.: "Disturbances of Rate and Rhythm in Acute Coronary Artery Thrombosis," *Ann. Int. Med.*, 11:735, 1937.

3 Totibouet, L. and Mathiut, A.: "Myocardial Infarction and Rhythm Disorders," *Arch. des Maladies Du Coeur*, 43:981, 1951.

4 Griffith, G. C.: Personal communication.

5 Gross, L.: *Blood Supply of the Heart in its Anatomical and Clinical Aspects*, 1931, Paul B. Hoeber, Inc., New York, p. 36.

6 Bellet, S.: *Clinical Disorders of the Heart Beat*, 1953, Lea and Febiger, Philadelphia.

7 Askey, J. M.: "Auricular Paroxysmal Tachycardia in Association with Myocardial Infarction," *Am. Heart J.*, 37:425, 1951.

8 Dameshek, W., Loman, J. and Myerson, A.: "The Effect on the Normal Cardio-

vascular System of Acetyl-Beta-Methyl Choline Chloride, Atropine, Progstigmine, Benzedrine—with Especial Reference to the Electrocardiogram,"*Am. J. M. Sc.*, 195:88, 1938.

9 Rosenbaum, F. F. and Levine, S. A.: "The Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction. I. Immediate Prognosis," *Arch. Int. Med.*, 68:913, 1941.

10 Middleton, W. S.: "The Prognosis and Treatment of Coronary Occlusion," *Minn. Med.*, 18:710, 1935.

11 Askey, J. M. and Neurath, O.: "Prognostic Significance of Auricular Fibrillation Occurring with Myocardial Infarction," *Am. Heart J.*, 29:575, 1945.

12 Bollings, F. T., Kalstone, B. M., Spencer, J. L., Ball, C. O. and Meneely, G. R.: "Prognosis of Acute Myocardial Infarction," *Am. J. Med.*, 7:356, 1940.

13 Wood, F., Wolferth, C. C. and Bellet, S.: "Infarction of the Lateral Wall of the Left Ventricle," *Am. Heart J.*, 16:387, 1953.

14 Cushing, E. H., Stanton, E. J. and Wartman, W. B.: "Infarction of the Cardiac Auricles (Atria). Clinical, Pathological and Experimental Studies," *Brit. Heart J.*, 4:17, 1942.

15 Goldman, M. J.: "Cardiac Arrhythmias in Myocardial Infarction," *Am. Heart J.*, *39:984, 1950.*

16 Master, A., Dack, S. and Jaffe, H. L.: "Partial and Complete Heart Block in Acute Coronary Occlusion," *Am. J. M. Sc.*, 196:513, 1938.

17 Graybiel, A. and White, P. D.: "Complete Auriculoventricular Dissociation," *AM. J. M. Sc.*, 192:334, 1936.

18 Hellmuth, G. A.: "Cardiac Arrhythmias-Pathology, Physiology, Diagnosis and Treatment," *Med. Clin. N. A.*, *36:3, 1952.*

19 Cooke, W. T. and White, P. D.: "Paroxysmal Ventricular Tachycardia," *Brit. Heart J.*, 5:33, 1943.

20 Amburst, C. A., Jr. and Levine, S. A.: "Paroxysmal Ventricular Tachycardia; A Study of One Hundred and Seven Cases," *Circulation*, 1:28, 1950.

21 Schlichter, J. G.: "Etiology of Auricular Fibrillation and the Mechanism of its Perpetuation," *Am. Heart J.*, 37:674, 1949.

22 Luisada, A. A.: "Coronary Heart Disease and Myocardial Infarction," *Med. Clin. N. A.*, 36:69, 1952.

23 Harris, A. S.: "Delayed Development of Ventricular Ectopic Rhythm Following Experimental Coronary Occlusion," *Circulation*, 1:1318, 1950.

24 Askey, J. M.: "Present Status of Digitalis in Therapy," *Ann. West. Med. and Surg.*, 2:66, 1948.

25 Gilson, J. S. and Schemm, F. R.: "Use of Digitalis in Spite of the Presence of Ventricular Tachycardia," *Circulation*, 2:278, 1950.

CURRENT THERAPY

The Editorial Board invites your comment.

Rest in Myocardial Infarction*

It is generally agreed that rest is a mandatory adjunct in the treatment of acute myocardial infarction. Any injured body tissue is known to heal more rapidly if the part is kept at rest, and since the injured myocardium must obviously continue to work while it is healing, it seems only rational to keep the work load as light as possible by the avoidance of any activity which would call for an increased cardiac output. There are a few physicians who treat patients with acute infarctions on an ambulatory basis; however, we feel that this procedure definitely entails an increased risk to the patient, to say nothing of the increased risk to the doctor if the patient's family is at all inclined toward malpractice suits. The main points of contention in regard to rest in this disease involve the questions, where, how, and how long.

It is our policy to hospitalize all cases of established or "impending" myocardial infarction for a period at least long enough to permit thorough evaluation. Hospitalization facilitates closer observation of the patient which renders easier the classification into "good risk" or "poor risk." It is much easier to obtain the desired laboratory work including electrocardiograms in the hospital, adequate treatment is more readily obtained, and any complication is likely to be detected much earlier. Some physicians have advanced the argument that it is dangerous to move a patient with an acute infarct to a hospital, particularly if shock is present, but we maintain that the presence of shock is an additional strong reason for getting the patient into the hospital as quickly as possible. This statement is made on the assumption that adequate ambulance service is available, including attendants to carry the patient, and oxygen equipment. It is seldom, if ever, necessary for the ambulance to rush to the hospital at full speed with siren screaming; most urban patients live within a few miles of a hospital, and the few minutes saved by rushing do not compensate for the increased discomfort to the patient. In the case of the rural population, it is probably true that very long ambulance trips should be avoided even if the patient must be treated in the home. This is becoming less of a problem, however, as more hospitals are being constructed in the smaller communities.

If a patient is established as a good risk case, he may be treated in the home after one or two weeks in the hospital, but if he is considered a bad risk or if any complication develops, he is kept in the hospital for four weeks or longer if necessary. We also keep all patients receiving anticoagulants in the hospital for the duration of such therapy. We have found that the desired degree of rest is often more readily and more uniformly enforced in the hospital: on one occasion one of us was unable to see a patient with an acute infarction when a visit was made to his home at an unexpected time because he was out for a ride!

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*From the Departments of Medicine, Divisions of Cardiology, Ohio State University College of Medicine and White Cross Hospital, Columbus, Ohio.

Our patients with acute coronary occlusion are kept at bed rest from three to six weeks depending upon the severity of the case. The presence of the factors enumerated by Russek[1] and others which cause the patient to be classified as a bad risk will generally keep him in bed longer. On the other hand, the good risk patient is often allowed to use a bedside commode for bowel movements provided he is assisted, and he remains in bed a shorter length of time. During the first two weeks after onset we are more conservative in regard to rest even when dealing with the good risk patient; this period is regarded as a crucial one in the course of this disease. We agree with White[2] that undue activity increases the incidence of ventricular rupture during the first two weeks, and while a certain number of patients will expire in this period regardless of the treatment employed, it is better for them to die in bed than on the floor.

Since Levine's[3] advocacy of the "chair treatment" for myocardial infarction, there has been considerable discussion concerning this type of rest. We feel that the argument of bed rest versus chair rest is more apparent than real: there is little difference between our patient with the head of his bed elevated and the foot lowered and the patient sitting in a chair. We do not favor the chair rest because of the increased demands upon hospital personnel that lifting the patient in and out of bed entails; also, if a patient thinks he is well enough to sit in a chair, he may tend to think he is well enough to walk about or to do other things that he should not be doing. It should be noted that in most instances hospital bed rest is far from the "absolute bed rest" that is commonly ordered: most patients will move about in bed considerably; in fact, if they do not do so of their own accord, they should be encouraged to at least exercise their arms and legs to some extent. This of course does not apply to patients in shock or to those with extreme chest pain. In regard to the latter, we doubt that others would get these patients up in a chair, either.

It has been claimed that extended bed rest is harmful because it favors the development of thromboembolic phenomena. Our experience lends no support to this thesis; rather, it tends to disprove it. In our series[4] of 386 cases of acute myocardial infarction treated with relatively strict bed rest, and *without anticoagulants*, thromboembolic phenomena occurred in eight (2 per cent). Thrombophlebitis and phlebothrombosis have been extremely rare in our acute coronary patients, whether they received anticoagulants or not.

Diet has a bearing upon the ratio of cardiac rest to cardiac work, and this aspect of diet seems appropriate for inclusion in this discussion, even though the broader subject of diet in coronary disease is beyond the scope of this paper. It is well known that during the digestive process the supply of blood to the organs of digestion is increased to a considerable extent, hence, it is logical to restrict the diet both as to quantity and quality. The diet should be of the low calorie, low residue variety and a liquid diet may be advisable if the patient is critically ill. One objective should be to avoid straining at stool, since the exertion required by the latter may lead to serious consequences. Since patients at rest seem to have an inordinate amount of difficulty with gaseous distention of the gastrointestinal tract which in turn interferes with rest, foods which are prone to generate gas should be avoided. During the convalescent stage when the patient is semi-ambulant a light diet is preferred, and it is considered advisable for the patient to rest for at least a half hour after each meal in order to avoid the extra demands upon the heart resulting from digestion and exercise simultaneously.

Narcotics and sedatives may be necessary to secure adequate rest in an individual with pain, dyspnea, or extreme apprehension, but we feel that they are often prescribed far too freely; they are even prescribed routinely by some physicians. While we believe that rest is necessary, we see no reason to give narcotics to the patient who has become relatively asymptomatic merely to depress his activity to a rigor mortis level. In fact, as we have already inferred, such a procedure is probably harmful as it could lead to a higher incidence of thromboembolism. We have found the so-called tranquilizers to be of some value in helping the patient secure proper rest, but here again a word of caution is necessary: when prescribed they should be given under close supervision, particularly during the initiation of therapy when the patient's reaction to them is unknown. Some of the tranquilizers may have rather marked hypotensive effects in certain patients; we have observed two patients with acute infarcts who suffered a sudden drop in blood pressure and went into refractory shock subsequent to the initial dose of the drug.

JAMES J. CONN, M.D., F.C.C.P. and R. W. KISSANE, M.D., F.C.C.P.
Columbus, Ohio

REFERENCES

1 Russek, H. I., Zohman, B. L., Doerner, A. A., Russek, A. S. and White, L. G.: "Indications for Bishydroxycoumarin (Dicumarol) in Acute Myocardial Infarction," *Circulation*, 5:707, 1952.

2 White, P. D.: *Heart Disease*, 3rd ed. New York, MacMillan, 1947, p. 501.

3 Levine, S. A. and Lown, B.: "Chair Treatment of Acute Coronary Thrombosis," *Tr. A. Am. Physicians*, 64:316, 1951.

4 Kissane, R. W., Fidler, R. S. and Conn, J. J.: "The Incidence of the Thromboembolic Phenomena Associated with the Treatment of Acute Coronary Occlusion," *Am. J. Med. Sci.*, 227:663, 1954.

THE ELECTROCARDIOGRAM OF THE MONTH

The authors would be pleased to receive comment and controversy from readers in relation to explanations offered.

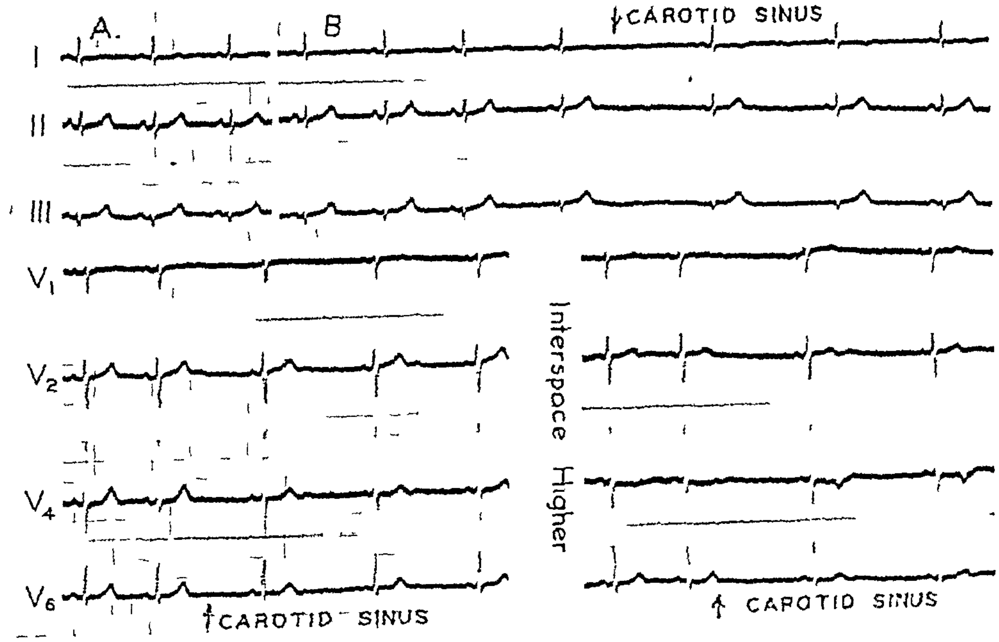
This electrocardiogram was obtained from a 58 year old white woman three days following an attack of severe pain in the chest. The pain did not radiate to the arms or any other characteristic area. There was no fever, no leucocytosis, and no increase in the sedimentation rate. She is not hypertensive and she does not have diabetes. The pain did not recur so that there was no opportunity to study an electrocardiogram made during pain at this time. Employing a polychannel apparatus electrocardiograms were recorded before and during carotid sinus stimulation. This was repeated with a second set of precordial leads made one interspace higher on the chest.

Interpretation

The original record A is not dissimilar to many normal electrocardiograms, even though T3 is higher than T1 in the presence of slight left axis deviation. If aVL had been recorded it would have shown an inverted T wave, but this finding means no more than the fact that TIII is greater than TI and is also encountered in many normal electrocardiograms. When we increased cycle length by carotid sinus stimulation the T wave in lead I became inverted while in leads V4 and V6 it became diminished in height and notched. When precordial leads were repeated at a higher level carotid sinus stimulation resulted in a definite inversion of a previously low T wave in V4 (itself a suspicious finding).

The record shows the value of studying the T waves of the electrocardiogram at different cycle lengths and how this can be accomplished by carotid sinus stimulation. In normal hearts a similar change in cycle length usually causes no change in the T waves or a slight increase *in their size. Such a change as is recorded here is certainly more diagnostic of ischemia than is the record A alone. At the same time it should be observed that a slight lowering of the T wave in the left precordial leads when it occurs in older persons with carotid sinus slowing may not be of clinical significance. One must also warn against mistaking changes due to change in the respiratory phase for changes due to cycle length change. Many persons are apt to take a deep breath when the carotid artery is compressed.*

MANUEL GARDBERG, M.D. *and* IRVING L. ROSEN, M.D.*
New Orleans, Louisiana



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*Cardiac Research Laboratory, Touro Infirmary and the Department of Medicine, Louisiana State University Medical School.

Case Report Section

Xanthogranuloma as a Coin Lesion of the Lung*

JOSE A. ALEGRE, M.D. and JOHN DENST, M.D., F.C.C.P.
Denver, Colorado

Isolated pulmonary xanthomatous nodules which present as coin lesions are uncommon. The gross resemblance of the lesion to a neoplasm and the peculiar microscopic characteristics, especially as seen in frozen sections, may lead to diagnostic errors. The following two cases are similar to those classified as xanthomas and reported by Scott, Morrow, and Payne[1] in 1948 and by Ford, Thompson, and Blades[2] in 1950. The lesion appears to be identical with the xanthogranulomas in the retroperitoneal region as described by Oberling[3] in 1935.

Case 1: (11087) A 10-year-old white boy was admitted to the National Jewish Hospital at Denver because an asymptomatic round mass was found in the upper lobe of the right lung by x-ray film six months before (Fig. 1). He was treated with streptomycin and para-aminosalicylic acid on the assumption that it was a solid tuberculous focus. Physical examination was negative. The x-ray picture remained unchanged, and the tuberculin, histoplasmin, and coccidioidin skin tests were negative. Laboratory procedures were negative; blood lipid studies were not done. At thoracotomy, a discrete nodule was shelled from the upper lobe of the right lung. As frozen sections showed a highly cellular lesion, this lobe was then resected. Recovery was uneventful.

The specimen consisted of a soft resilient pale yellow unencapsulated nodule which measured 2.5 x 3 cm. The right upper lobe appeared to be normal except for a cavity in the apical segment from which the lesion had been enucleated. Microscopically, the mass consisted of sheets of spindle-shaped and oval cells in fascicular arrangement with small blood vessels interspersed (Figs. 2 and 3). The nuclei were relatively large and vesicular with one or two nucleoli. Some nuclei were hyperchromatic. The cytoplasm was pale with faint minute vacuoles. Some syncytial-like groups of larger cells were scattered throughout, but typical reticulated xanthoma cells and giant cells were not observed. Occasional eosinophils and lymphocytes were present. Scharlach R. fat stain unexpectedly revealed large amounts of lipoid within the great majority of both the spindle and oval cells. Reticulum fibers outlined the many small blood vessels, and, in some fields, coarse parallel fibers were present among the cells containing lipid. The elastic fiber Van Gieson stain failed to reveal mature collagen or elastic tissue. The Weil and Bodian stains showed no nerve fibers. The margin of the lesion in the separately resected right upper lobe consisted of a fairly discrete zone of granulation tissue with many foam cells, neutrophils, plasma cells, nodules of lymphocytes, and relatively little collagen. The mucosa of an apical segmental bronchial branch was involved in the reaction.

Case 2: (89366) A 17-year-old white boy entered Colorado General Hospital for resection of a round lesion in the right lower lung field just above the diaphragm, which was found in a routine radiograph. Physical examination and routine laboratory studies revealed no abnormality. Blood lipid levels were not obtained. At thoracotomy, a sharply circumscribed spherical nodule, unrelated to bronchi, was shelled from the lower lobe of the right lung. His postoperative course was uneventful.

The specimen consisted of a gray-yellow, homogeneous, soft, slightly bosselated spherical nodule measuring 1.8 cm. in diameter. Microscopically, it was composed of compact fasciculated spindle-shaped or oval cells with finely vacuolated cytoplasm. The nuclei were plump, pale or darker, with fine evenly distributed chromatin. Lymphocytes, plasma cells, and larger histiocytes were scattered throughout. Typical large xanthoma cells were numerous in several fields (Fig. 4). The reticulum stain outlined many small blood vessels throughout the lesion, but fibers between cells were rare. Mature collagen was present only in occasional patchy peripheral foci.

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*From the National Jewish Hospital at Denver, and the Department of Pathology of the University of Colorado School of Medicine.

Discussion

These discrete soft pale yellow nodules were composed predominantly of spindle-shaped cells which resembled fibroblasts. For this reason the diagnosis of a fibroblastic tumor was suggested. However, stains for connective tissue revealed only rare foci of collagen. One of the lesions contained intercellular reticulum; reticulum fibers were generally confined to walls of the many small blood vessels. It is of interest that a significant component of collagen was absent in the lesion of a previously reported case.[2] The abundance of lipoid material was recognized only with the use of the stain for fat. The phagocytic character of the cells might have been suspected from the fine foamy cytoplasmic vacuolation of most of the cells. Typical xanthoma cells were present in a few fields in Case 2; giant cells were absent. Leukocytes were present in varying numbers. The pulmonary framework was destroyed; the mucosa of a bronchial branch was partly replaced with granulation tissue.

We have classified these lesions as xanthogranulomas because they appeared to represent a genuine granulomatous reactive process, basically identical with that described by Oberling[3] in three retroperitoneal lesions. The relationship of the pulmonary form of the disease with the retroperitoneal lesions was pointed out by Stout[4] who studied material from Case 1. Stout[5] noted the occurrence of xanthogranulomas in the mediasti-

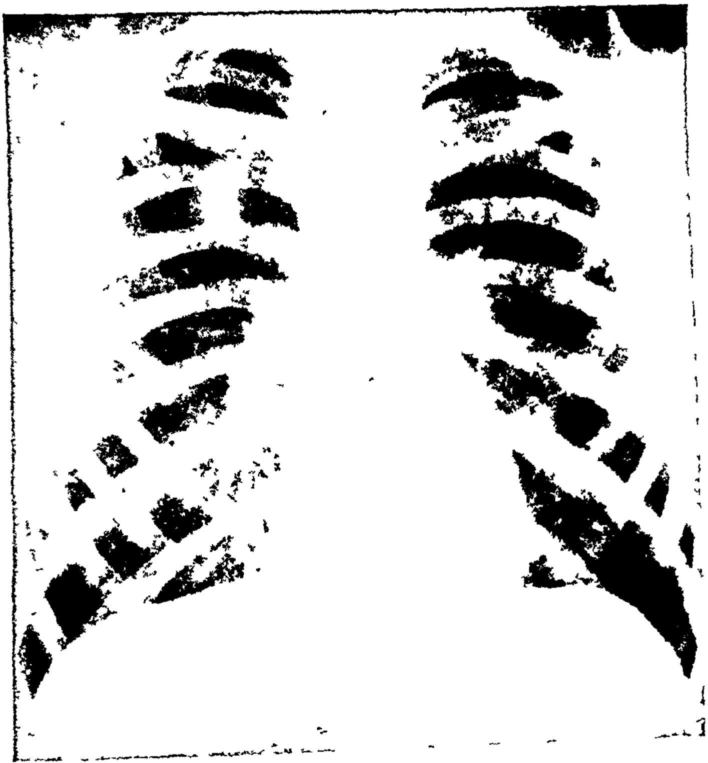

FIGURE 1 (Case 1): X-ray taken six months prior to admission.

num and mesentery as well as in the lung and retroperitoneal region. Although the term xanthogranuloma does not emphasize the pseudoneoplastic quality of the process, we prefer it to others which have been used. The term xanthoma indicates a uniform proliferation of characteristic foam cells. Fibroxanthoma or xanthofibroma seem to be less appropriate terms as they imply a neoplastic origin, and collagen fibers also are sparse in the nodules.

Oberling stated that xanthogranulomas are frankly inflammatory, consisting of more or less extensive infiltrations of macrophages, lymphocytes

FIGURE 2

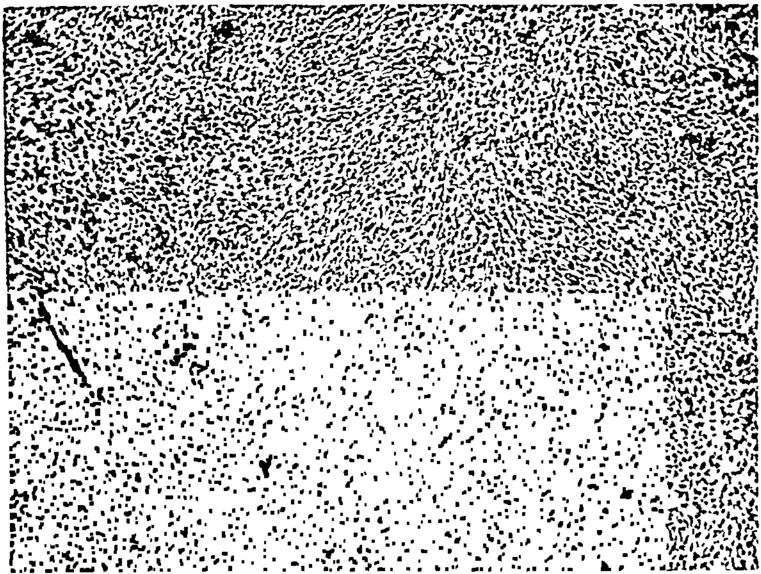

FIGURE 3

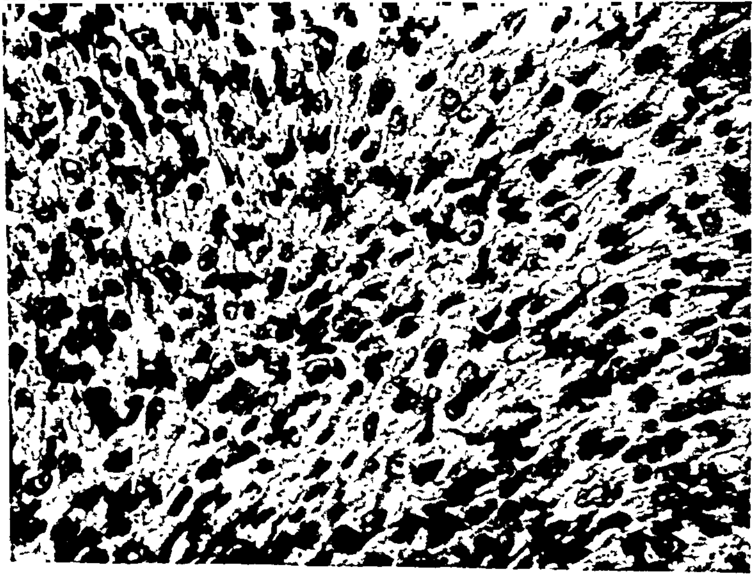

Figure 2 (Case 1): Bundles of spindle-shaped cells. H. & E. ×100.—*Figure 3* (Case 1): The foamy character of the cytoplasm of the elongated cells is shown. H. & E. ×400.

and plasma cells, areas of sclerosis, and invariably foam cells containing neutral fat and cholesterol. One of his three cases exhibited a pseudosarcomatous pattern. He related the disease to that of Hand-Schuller-Christian and noted that such isolated granulomas had been described in bones, lymph nodes, the stomach, and elsewhere. He considered them to be distinctly different from the xanthomas of skin, tendon sheath, and joints which were associated with jaundice, diabetes, or generalized disturbances of fat metabolism. They were not simply a reaction to lipid such as occurs in Niemann-Pick's disease. They also differed from the xanthomatous transformation of nerve sheath tumors. Oberling further believed that local irritative inflammation and derangement of cholesterol metabolism were both significant factors in pathogenesis. In his cases as in ours no clue to a specific infective agent was noted.

More recently, Umiker and Iverson[6] added three intrapulmonary postinflammatory "tumors" to the literature and included those of Scott et al,[1] Ford et al,[2] Csermely's[7] case of xanthofibroma, and Childress and Adie's[8] plasma cell tumor in a review of the problem. They considered that all of these lesions were inflammatory on the basis of microscopic appearance or history. If one cell predominated, they simulated xanthoma, fibroxanthoma, neurofibroma, vascular tumor, or plasma cell tumor. These nodules were similar to three nonxanthomatous lesions of the pleura described by Brown and Johnson.[9] We believe that the lesions we have called xanthogranulomas are the same as several of the postinflammatory "tumors". Nevertheless, as the xanthomatous feature was dominant, the

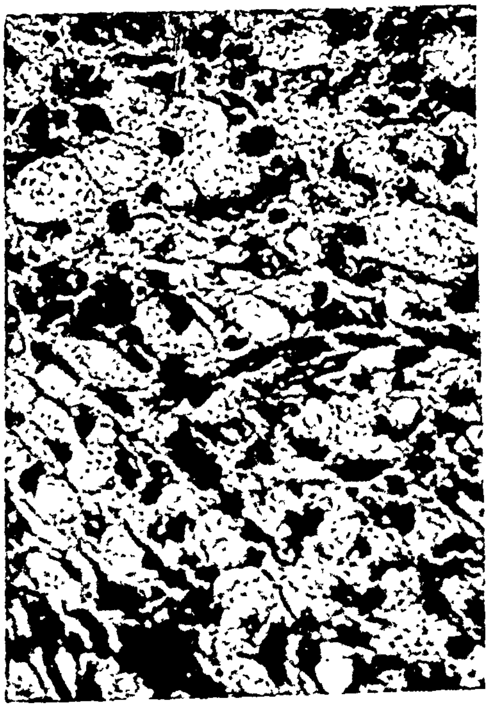

FIGURE 4 (Case 2): Field of typical xanthoma cells. H. & E. × 400.

more specific descriptive diagnosis of xanthogranuloma appears to have merit, at least in certain cases.

The sclerosing hemangiomas of the lung reported by Liebow and Hubbell[10] also showed xanthomatous elements. These vascular lesions, regarded as analogous to those of the skin, exhibited hemorrhages, papillary infoldings, and obliteration of air spaces with atypical proliferation of lining cells. The authors concluded that the relationship to the so-called xanthomas or postinflammatory "tumors" must be considered tentative.

Two cases of a peculiar xanthomatous nodule of the lung have been reported because their superficial resemblance to a neoplasm offers a diagnostic problem and because they probably will be observed more frequently with the increasing tendency to extirpate coin lesions. They are termed xanthogranulomas because of the basic granulomatous nature of the cellular proliferation, the heavy lipoid content of the constituent cells, and the similarity to the lesion as seen in other locations. These two cases appear to be either variants or identical with the other seven cases in the literature which have been called postinflammatory "tumors" by Umiker and Iverson. The inflammatory origin seems to be common to all. Oberling believed local inflammation and a derangement of cholesterol metabolism were important. Association with a general disturbance of lipoid metabolism has not been noted in any of the cases, although sufficient laboratory investigations have not been made to exclude this possibility. As yet there is no certainty that the lesions are related to Hand-Schuller-Christian disease as considered by Oberling or to eosinophilic granuloma of the lung. The prognosis appears to be good, and symptoms are either absent or mild.

REFERENCES

1 Scott, H. W., Jr., Morrow, A. G. and Payne, T. P. B.: "Solitary Xanthoma of the Lung," *J. Thor. Surg.*, 17:821, 1948.

2 Ford, W. B., Thompson, C. W. and Blades, B.: "Xanthoma of the Lung," *Postgrad. Med.*, 8:48, 1950.

3 Oberling, C.: "Retroperitoneal Xanthogranuloma," *Am. J. Cancer*, 23:477, 1935.

4 Stout, A. P.: Personal Communication.

5 Stout, A. P.: "Tumors of the Soft Tissues," Atlas of Tumor Pathology, Sect. II, Fascicle 5, p. 28, 1953, Armed Forces Institute of Pathology.

6 Umiker, W. O. and Iverson, L.: "Postinflammatory 'Tumors' of the Lung; Report of Four Cases Simulating Xanthoma, Fibroma, or Plasma Cell Tumor," *J. Thor. Surg.*, 28:55, 1954.

7 Csermely, H.: "Xanthofibroma Pulmonis," *Zentralbl. Allg. Path.*, 78:118, 1941-42.

8 Childress, W. G. and Adie, G. C.: "Plasma Cell Tumors of the Mediastinum and Lung; Report of Two Cases," *J. Thor. Surg.*, 19:794, 1950.

9 Brown, W. J. and Johnson, L. C.: "Postinflammatory 'Tumors' of the Pleura," *Mil. Surg.*, 109:415, 1951.

10 Liebow, A. A. and Hubbell, D. S.: "Sclerosing Hemangioma (Histiocytoma, Xanthoma) of the Lung," *Cancer*, 9:53, 1956.

Spontaneous Mediastinal Emphysema with Bilateral Pneumothorax as a Complication of Bronchopneumonia*

J. HEICHMAN, M.D., G. FIALKOV, M.D. *and* A. JUNGMANN, M.D.
Haifa, Israel

Spontaneous mediastinal emphysema with bilateral pneumothorax as a complication of bronchopneumonia has not, to our knowledge, so far been reported in the literature.

Gray[4] in 1919 presented a case of bilateral spontaneous pneumothorax occurring in the course of advanced bilateral tuberculosis after which the patient soon died. In a second case of spontaneous mediastinal emphysema with bilateral pneumothorax,[6] no clinical or radiological findings which could explain the etiology were discovered.

This 17 year old boy was born in Israel. Family and past history were irrevelant. He fell ill a week before admission to the Haifa Rambam Hospital, complaining of pyrexia, headache and chest pains which increased on deep inspiration. His general condition was fair until 24 hours prior to admission when he suddenly felt worse.

On the day prior to admission there had been a sudden attack of severe cough, followed by intense pain in the centre of the chest, accompanied by marked dyspnoea.

On examination he appeared acutely ill, and had severe dyspnoea, orthopnoea and considerable cyanosis of lips, ears and fingertips. Pronounced râles during respiration were heard from a distance and scummy spittle was dripping from his mouth. The clinical picture resembled that seen in pulmonary edema. He was restless and mumbling unintelligibly.

His blood pressure, when first examined, was 150/0, pulse-rate 130 and temperature 38° C. Moist râles were heard in both lungs which made it difficult to hear the heart-sounds or to define their nature. The breath-sounds over both upper lung fields were diminished and on percussion cardiac dullness could not be determined.

The abdomen and extremities were negative.

ECG findings on admission: sinus tachycardia 148'. High P in the leads L II, L III and AVF and negative in AVL. (An ECG four days later showed normal findings.)

He was immediately given 0.5 mg. strophantin and 0.01 morphine intravenously and was placed in an oxygen tent, but almost no change in his condition was observed.

During the night a venopuncture of 500 cc. was performed and his condition improved slightly. The next day the respiratory distress was still present and there was a tachycardia of 130 per minute. The temperature remained unchanged and the blood pressure was then found to be 140/80.

Subcutaneous emphysema was found in the region of the neck and above the clavicles on both sides. Cyanosis persisted and the respiratory sounds remained weak in the apical regions. There was hyperresonance to percussion over both lungs.

In the region of the midchest, strange, crunching breath-sounds were heard, as well as noises resembling the bursting of toy balloons. These unusual sounds were best heard above the precordial area. He complained of oppression of the chest and difficulty in breathing, which was aggravated by every movement.

The x-ray film examination of the chest showed pneumothorax on the right side with compression of the entire lung by a mantle of air, about 2 cm. in width. On the left there was pneumothorax in the apical region. Mediastinal emphysema and subcutaneous emphysema of the neck and the supraclavicular areas were seen.

The lung fields showed a veiling, composed of soft, ill-defined patches with a dense and almost homogeneous clouding at the base of the right lung and in the left upper lung field.

These findings suggested bilateral bronchopneumonia, mediastinal emphysema, bilateral pneumothorax and subcutaneous emphysema.

Throughout the day his condition remained poor. He was cyanotic and considerably dyspnoeic and as there seemed to be no tendency to improve, pleural puncture was performed in the evening. The needle was introduced first on the right side and the intrapleural pressure was found to be 140 mm. Hg. Approximately 1,000 cc. of air was withdrawn and the pressure came down to —0. The same procedure was carried out on the left, the pressure was 10 mm. Hg., and after withdrawal of 400 cc. of air it decreased to —0. His condition improved immediately.

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* "Rambam" Government Hospital.

An x-ray film at that stage showed no pneumothorax on the right side, but there still was air over the left apex. The mediastinal and subcutaneous emphysema remained unchanged and the lungs still showed the bronchopneumonic infiltrations.

His general condition continued to improve, but the temperature remained elevated in spite of continuous treatment with penicillin and streptomycin. The temperature subsided only after chloromycetin treatment was begun. Repeated throat and sputum smears revealed pure cultures of staphylococcus aureus sensitive only to chloromycetin.

X-ray films on the third day of hospitalization showed many ill-defined and confluent, soft infiltrations on both sides. There were still remnants of the pneumothorax at the left apex, pneumo-mediastinum and subcutaneous emphysema in the cervical region. There was no further important roentgenological change on the fourth day. On the seventh day the x-ray film still showed evidence of bronchopneumonic infiltrations, but no more signs of the pneumothorax or the mediastinal and subcutaneous emphysema. On the 16th day of hospitalization no evidence of chest disease was found.

The clinical entity of spontaneous mediastinal emphysema has been known for many years.[1] Apart from those cases, in which mediastinal emphysema appears following trauma or operation, and which should not in a strict sense be described as "spontaneous," there are many other possibilities as to its etiology: Its occurrence as a complication of infections (tuberculosis, pneumonia, diphtheria, influenza, measles, pertussis, asthma, during labour[3, 4, 10] and in obstructive emphysema) has been described, but there remain not infrequent cases in which the cause is unknown and which are designated as "idiopathic."

The most striking clinical finding is known as "Hamman's syndrome" or "sign," which is described as a loud, crunching, crackling, snapping, crepitant sound, synchronous with the heart beat.[5] Cardiac dullness is partly or completely obliterated. Mediastinal emphysema is often accompanied by pneumothorax, most commonly found in the left upper region. The latter is described in nearly all cases as being so limited as to be detected only on x-ray film.

Various clinical symptoms, often contradictory, are described by different authors, possibly on account of the respective varying etiology. On the other hand, the clinical manifestations are largely due to the measure of the physical changes, i.e., the amount of air in the mediastinum or the size of the pneumothorax. Since the number of cases seen by individual authors is generally small, generalizations in their description were sometimes used, which were perhaps not quite justified by these sporadic observations.

One of the main and most common symptoms is a sudden severe pain in the chest, which may disappear within hours, but might continue for days, and which, depending on its immediate cause, i.e., the amount and localization of mediastinal air, may even simulate an attack of angina pectoris. The pain, in the opinion of some authors,[2, 7, 10] et al is caused chiefly by the pressure of air which intruded suddenly between the heart and the anterior chest wall. Its presence in large amounts, according to them, is liable to cause compression of the heart and large vessels. These authors explain that encroachment upon the space occupied by the pulmonary vessels interferes with the circulation through the lungs and may result in embarrassment to the right heart. In this case, Klein[7] reports that characteristic ECG findings of acute right ventricular strain are demonstrated, whereas Stein[10] found that there are no typical electrocardiographic changes in this condition.

Again, while Klein[7] describes the above mentioned right heart strain and others confirm the occurrence of cyanosis as a rather frequent symptom. Schendstock[9] reports that "shock and cyanosis do not occur" and Miller[8] came to the conclusion that "dyspnoea, cyanosis and orthopnea may occur, but are not characteristic."

CONCLUSIONS

The presentation and discussion of this case appears justified for the following reasons:

a) The rare occurrence of the syndrome;
b) The typical clinical findings which could lead to its correct diagnosis;
c) The possibility of a specific treatment consisting of the withdrawal of air from the pleural cavity in order to decrease the extent of the pneumothorax.

The marked release from discomfort, which the patient experienced following this intervention is astonishing, if compared to the comparative ease with which therapeutic pneumothorax is tolerated, even though the amount of air which is normally introduced is generally far greater than was found in this case. The explanation for this discrepancy is believed by us to be the simultaneous mediastinal emphysema, which causes compression of the heart and thereby diminished cardiac output with resulting circulatory failure, together with the pressure exercised by the pneumothorax upon the distended mediastinum. We have no explanation for the blood pressure abnormality, which on repeated examinations at the time of admission was found to be similar to that seen usually in aortic insufficiency, arterio-venous fistula, etc., and which returned to normal later on.

REFERENCES

1 Aisner, M. and Franco, J. E.: "Mediastinal Emphysema," *New England J. Med.*, 241:818, 1949.

2 Evans, J. A. and Smalldon, T. R.: "Mediastinal Emphysema," *Am. J. Roentgenol.*, 64:375, 1950.

3 (a) Fridjohn, L. and Azzopardi, P. G.: "Acute Mediastinal and Subcutaneous Emphysema," *Lancet*, 1:904, 1949. (b) Kahn, J. S. and Rouse, J. W. H.: "Interstitial Mediastinal Emphysema Due to Bronchial Asthma," *J. Allergy*, 22:111, 1951. (c) MacRae, D. J.: "Spontaneous Pneumomediastinum in Pregnancy," *Lancet*, 1:902, 1949. (d) Nielsen, J. A.: "Mediastinal and Subcutaneous Emphysema in Two Siblings with Measles," *Ugesk. Laeg.*, 116:665, 1954.

4 Gray, E. A.: *Ill. Med. J.*, 35:252, 1919, quoted from Fishberg, M.: "Pulmonary Tuberculosis," Philadelphia and New York, 1922, p. 526.

5 Hamman, L.: "Spontaneous Mediastinal Emphysema," *Bull. Johns Hopkins Hospital*, 64:1, 1939.

6 Hyde, B. and Hyde, L.: "Spontaneous Mediastinal Emphysema and Bilateral Spontaneous Pneumothorax," *Am. Rev. Tuberc.*, 61:883, 1950.

7 Klein, A.: "Spontaneous Mediastinal Emphysema with Acute Right Ventricular Strain," *Am. Heart J.*, 33:867, 1947.

8 Miller, H.: "Spontaneous Mediastinal Emphysema," *Ann. Int. Med.*, 21:998, 1944.

9 Schendstock, J. D.: "Recurrent Spontaneous Emphysema of the Mediastinum with Concomitant Pneumothorax: Report of a Case," *New England Med. J.*, 235:511, 1946.

10 Stein, M. H.: "Spontaneous Mediastinal Emphysema," *N. Y. State J. Med.*, 45:1659, 1946.

Chemotherapy of Specific Infectious Diseases of the Lower Respiratory Tract

Report of Committee on Chemotherapy and Antibiotics
American College of Chest Physicians

The majority of pulmonary infections can be successfully treated by the judicious use of antibiotics and other chemotherapeutic agents. It is important to establish a diagnosis of the type of infection in all infectious diseases of the respiratory tract. Cultures should be made prior to therapy whenever feasible. Sensitivity tests of the organisms found in all prolonged infections are essential guides in the care of the patient. It is sometimes difficult to make an exact bacteriological diagnosis at the onset of a pulmonary infection, and treatment may have to be started at once. A simple Gram's stain of a fresh sputum specimen is important in determining the type of therapy while awaiting the cultures. If the diagnosis is still obscure and the patient has a severe infection, therapy designed against both gram-positive and gram-negative organisms should be instituted. Obviously all other clinical guides will be useful, such as the manner of onset of the disease, the characteristics of the sputum, the white count, the cold agglutinins, etc. Treatment should be vigorous and should be continued until all signs of infection have cleared. This is important to prevent development of chronic disease of the lungs and bronchi.

Classification of Pneumonias

I. *Bacterial*
  a. Pneumococci
  b. Streptococci
  c. Staphylococci
  d. Klebsiella Pneumoniae
  e. Hemophilus Infections
    1. Pertussis
    2. H. Influenzae
  f. Pasteurella Infections
    1. Pasteurella Pestis
    2. Pasteurella Tularensis
  g. Coliform, Proteus and Pseudomonas (gram-negative bacilli present in the intestinal tract)
  h. Salmonella Group
    1. Typhoid
    2. Paratyphoid A.B.C.
  i. Brucella
  j. Anthrax
  k. Glanders

II. *Viral* (Known and Probable)
   a. Psittacosis
   b. Influenza A & B
   c. Variola
   d. Varicella
   e. Rubella
   f. Lymphocytic Choriomeningitis
   g. Primary pneumonitis of infants
   h. Infectious mononucleosis
   i. Erythema Exudativum Multiforme
   j. Primary atypical pneumonia

III. *Rickettsial*
   a. Typhus
   b. Rocky Mountain Spotted Fever
   c. Q Fever

IV. *Mycoses* (Producing a pneumonia-like picture)
   a. Actinomycosis
   b. Nocardiosis
   c. Blastomycosis
   d. Coccidiodomycosis
   e. Histoplasmosis
   f. Moniliasis
   g. Cryptococcosis
   h. Aspergillosis
   i. Geotrichosis
   j. Penicilliosis
   k. Sporotrichosis

Treatment of Pneumonias

I. Bacterial Pneumonias

Pneumococcal Pneumonia. Penicillin is the drug of choice in the treatment of pneumococcal pneumonia. It is best given by the intramuscular route, using 300,000 units of aqueous penicillin every three to four hours, or 600,000 units of procaine twice daily. Oral penicillin is not advised except in mild cases. Therapy is continued until the temperature has been normal for three days. Larger or smaller doses may be used depending on the severity of the disease. The sulfonamides are highly effective in the treatment of pneumococcal pneumonia. The dosage is 6 to 8 gms. daily. The broad-spectrum antibiotics, including tetracycline, chloramphenical and erythromycin are all effective, but should still be considered second to penicillin.

Streptococcal Pneumonia. Treatment of streptococcal pneumonia is the same as that of pneumococcal pneumonia.

Staphylococcal Pneumonia. Treatment of staphylococcal pneumonia requires considerable care in view of increasing development of staphylococcal resistance to most antibiotics. Sensitivity tests should be made early. If the organism is penicillin sensitive, large doses of penicillin, two to four million units daily should be given and no other antibiotic need be given with it except perhaps streptomycin. If the organism is penicillin resistant and susceptible to erythromycin or novobiocin then one or the other of these drugs should be used. Vancomycin, which is not yet on the market, is an excellent bactericidal agent for staphylococci and should be used if the organism is resistant to other more readily available drugs. In the seriously ill patient who is not responding to the prescribed therapy, bacitracin in doses of 25,000 units every six hours should be added. The nephrotoxic potentialities of bacitracin must be watched. Treatment of staphylococcal infections should be prolonged for three or four weeks.

Klebsiella Pneumonia. Test of susceptibility should be performed but usually this type of pneumonia is best treated by streptomycin 2 to 4 gms. daily plus one of the tetracyclines in 4 gm. dosage initially. After response to therapy the dosage may be lowered. Sulfadiazine has also been quite effective in conjunction with streptomycin. Treatment must be continued for several weeks because of the severity and chronicity of the disease. The potential toxicity of streptomycin when used too long must be kept in mind.

Hemophilus Infections. Chloramphenicol or tetracycline in doses of 2 to 4 gms. daily are effective in both pertussis and H. influenzae infections. Sulfadiazine or streptomycin should be used in combination in the serious case.

Pasteurella Infections. Sulfadiazine, streptomycin, chloramphenicol and tetracycline have all proved effective in the treatment of plague pneumonia. Streptomycin is the drug of choice. Streptomycin is the ideal agent in the treatment of tularemic pneumonia in dosage of 2 to 4 gms. daily. The broad spectrum antibiotics are also effective.

Coliform, Proteus and Pseudomonas Group. This group is becoming increasingly important as a result of antibiotic therapy. Sensitivity tests must be done to find the most effective drugs. The organisms may be sensitive to the broad-spectrum antibiotics, sulfadiazine and streptomycin. A tetracycline may be sufficient for the coliform and proteus types of pneumonia if the organism shows susceptibility to these agents but combinations of antibiotics are usually necesssary. If these organisms are resistant combination of tetracycline and streptomycin in full dosage should be tried. If response does not occur penicillin, in large doses, in combination with chloramphenicol should be tried. In resistant infections polymyxin may be used with a tetracycline. Polymyxin is the drug of choice for pseudomonas pneumonia. The drug is both nephrotoxic and neurotoxic. It should be used with caution. In general, infections by this group respond poorly to all antibiotics.

Salmonella Group. The typhoid bacillus is a rare cause of pneumonia. Chloramphenicol 2 to 4 gms. daily followed in a few days by 1 gm. dose is specific. In the other Salmonella infections, chloramphenicol or one of the tetracyclines may be used.

Brucella Infections. Brucella infections are best treated by a combination of tetracycline, ¾ gm. every six hours in combination with streptomycin 1 gm. daily for a month.

Anthrax. Pulmonary anthrax is a rare complication of anthrax but when present is a very serious and fulminating disease. The tetracyclines are the drugs of choice, though penicillin and the sulfadiazines have also been used successfully.

Glanders. Lung lesions occur in about one-quarter of the glanders cases. Sulfadiazine and streptomycin are effective in the treatment of glanders. The broad-spectrum antibiotics have also been used successfully.

II. Viral Pneumonias

Psittacosis. The tetracyclines are the drugs of choice using 4 gms. daily for the first two days, followed by a 2 gm. daily dosage. Penicillin has been used successfully.

Virus Influenzal Pneumonia. There is no known specific for influenzal pneumonia.

Variola. Pulmonary lesions often occur in smallpox. There is no specific for the primary disease but because of secondary infections by bacteria appropriate chemotherapy for these infections should be used.

Varicella. Pneumonia occurs rarely. Treatment should be directed to secondary bacterial infections.

Rubella. Bronchopneumonia is a common complication of measles. While there is no specific for the measles virus, superimposed bacterial infections are frequent and can be successfully treated by penicillin or the tetracyclines.

Lymphocytic Choriomeningitis. Pneumonia occurs in lymphocytic choriomeningitis. Treatment is symptomatic.

Primary Pneumonitis of Infants. There is a serious disease in the newborn and premature infants probably due to a virus. There is no known specific therapy.

Infectious Mononucleosis. Bronchopneumonia is a rare complication of infectious mononucleosis. There is no known specific for this disease.

Erythema Exudativum Multiforme (Stevens-Johnson Syndrome). Pneumonia is a common accompaniment of this disease. It appears to be due to a virus which is not affected by any known antibiotic. Steroid therapy has often proven to be helpful.

Primary Atypical Pneumonia. The status of drug therapy of Primary Atypical Pneumonia is still under question. Some observers feel that a tetracycline 0.5 gm. every six hours should be given until temperature has been normal for at least three days, principally to guard against secondary bacterial invaders. Some observers prefer to use no antibiotic therapy in the average case unless there is indication of a secondary infection.

III. Rickettsial Pneumonias

Treatment of all of the rickettsial pneumonias may be combined together. Chloramphenicol or a tetracycline appears to be equally effective. The dosage in severe cases is 1 gm. every six hours for three doses, then 0.5 gm. every six hours until the temperature is normal.

IV. Mycotic Infections

Actinomycosis. Penicillin is the drug of choice, one or two or more million units a day usually along with surgical drainage if necessary. One of tetracyclines may be just as effective. Treatment is continued for at least six weeks and should be kept up long after the lesions have disappeared to prevent a recurrence.

Nocardiasis. Sulfadiazine is the drug of choice for nocardia infections. The broad-spectrum antibiotics may be helpful. The treatment must be prolonged.

Histoplasmosis. At present there is no proven therapeutic agent for this disease, but very suggestive results are being obtained with a new antibiotic, amphotericin B. The drug has been employed in a number of cases and the incidence of serious toxic manifestations has been relatively low. It has also demonstrated definite therapeutic effect. The drug is very difficult to administer and must be given intravenously in a slow drip over a period of six hours. Approximately 1 mgm. per kilo per day is the usual daily dose and treatment is continued from 30 to 60 days. Under special circumstances the daily dose may be increased to as much as 100 mgm. per day. An oral form of the drug is available, but has not proved to be effective. Immediate febrile complications during therapy are not unusual especially if the drug is given too fast. These effects may be ameliorated by aspirin. These reactions have not interfered with the continued use of the drug.

Blastomycosis. 2-hydroxystilbamidine is the most effective agent in the treatment of blastomycosis. Standard daily dose is approximately 250 mgm. dissolved in 250 to 500 cc. of 5 per cent dextrose, and given intravenously. This is given rather slowly over a period of several hours at least. The drug should be used immediately after preparation and the solution should be protected from sunlight. Thirty to sixty days of daily dosage of 250 mgs. is recommended. The drug may be repeated in case of a relapse. Facial neuropathy may occur but is much less frequent than with stilbamidine. Recently amphotericin B has appeared quite effective in treatment of Blastomycosis.

Coccidioidomycosis. Amphotericin B may be used for treatment of coccidioidal disease.

Moniliasis. Mycostatin is an effective antifungal drug for intestinal moniliasis, or it can be used locally. It has no effect on the systemic disease as it is not absorbed from the intestinal tract. In systemic moniliasis it is suggested that one of the newer antibiotics be employed, such as amphotericin B.

Cryptococcosis. Amphotericin B may be used. Its effectiveness is still under investigation.

Aspergillosis, Geotrichosis and Penicilliosis. These diseases are refractory to all known antibiotics. Amphotericin B should be tried.

Sporotrichosis. This usually responds satisfactorily to potassium iodide. 2-hydroxystilbamidine should be tried in the refractory case.

Steroid Therapy

The role of steroids in the therapy of infectious disease is a subject of tremendous controversy. When overwhelming infections cause adrenal insufficiency steroid therapy is indicated. The beneficial anti-inflammatory and "antitoxic" effect of the steroids is opposed by the adverse influence of the steroids on tissue localization of infection. However it is likely that one may accomplish the desirable and prevent the potential harmful effects of steroids by the simultaneous use of anti microbial agents to which the infective agent is susceptible. On theoretical grounds at least it would be undesirable to use steroid therapy in infections caused by organisms resistant to anti-microbial agents. There appears to be a place for the use of steroids in overwhelming infections not responding to conventional therapy.

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Editorial

"And he said unto him, if they hear not Moses and the prophets, neither will they be persuaded, though one rose from the dead." St. Luke, 16:31

The exemplary effort of the American College of Chest Physicians in sponsoring international congresses on diseases of the chest throughout the world has contributed to a most successful scientific interchange and has linked physicians around the globe in a spirit of understanding in non-medical fields. These ties have brought home to us that we are part of a corps of a million and a half men and women motivated by the ideal of conserving life. Even more closely must the ideal of conserving happiness unite us, for we cannot conceive of health without the happiness that springs from mental health. The physician is a champion of the struggle against disease, death and unhappiness.

In constant collision with the persistent, heroic and tireless labor of the physicians of the world is the menace of disease, death and unhappiness represented by war. War is an everyday theme; every day the newspapers speak of war; every day the motion pictures throw it on their screens; every day we listen to the radio, fearful lest some cultural program be interrupted by an announcement that the baleful tempest has been unleashed.

From all parts of the world, editorials in this journal — A. Omodei Zorini's from Italy, Jose Baldo's from Venezuela, Jay Arthur Myers' Arnold S. Anderson's and Andrew L. Banyai's from the United States, Richard R. Trail's from England, and Mohammed Ibrahim's from Pakistan — tell us eloquently how united are the aspirations and acts of physicians in furthering human understanding. No peaceful task is more rewarding than the discovery by combined effort of new arms against disease; no collaboration is greater than that which united Noguchi, Metchnikoff, Calmette, Fleming, Waksman, Finlay and many others.

Physicians, however, need no persuasion to appreciate the benefits of mutual interchange or the nobility of a united medicine. It is the masses and their leaders who need be persuaded of the truth in the ideals that we proclaim. Man must not go on working his own destruction, for armament in its present perfection can only lead to annihilation of the human race and an infinite retrogression of civilization.

When we are told that interplanetary space will soon be conquered and that the day is not distant when man will tread the moon, we turn disconsolate eyes to earthly conquests that concern us more closely; conquests of cancer, tuberculosis and the ever-increasing psychoses that fill half the hospital beds of the civilized world.

Profoundly disturbed, we see that the lunacies of civilization drive man to fratricidal combat, and that not even exposition of his motives offer a remedy for avoiding war. Man has begun to fear freedom. He escapes from liberty, as Fromm says, because he has created for himself a state of mind in which warlike tendencies enslave him.

This is the world's sickness. We physicians are accustomed to struggle with disease of individuals, but we have not yet confronted the problem of mass disease, the neurosis of agression that one can perceive in the mass subconsious mind. This is the problem that the medical profession finds before it. We must busy ourselves with its difficult solution, but how can we approach it with only our goodwill, our ethics and our unarmed, passive attitude? Precisely because we have these arms of kindness can we gradually modify the world, cause the masses to understand this evil and to face it.

Nothing is as good as going back and forth from one country to another, so that we may know and learn to love one another.

We are no prophets. Even Abraham recognized the futility of raising his voice to persuade people. We physicians must act by patiently spreading understanding among ourselves; we must foster international interchange and international aid in solving these problems. Wherever the physician can make his voice heard (and he has opportunities always and everywhere) his mission should be to promote mutual aid, of one country and one continent to another.

If strong and rich nations aid the dispossessed to rid themselves of the scourge of disease, their efforts will do more to promote peace than any other persuasive force.

We do not need more shipments of arms or money, but more help to conquer disease, ignorance and hunger in underprivileged countries! For it is desolating that while some may listen to the faint signals of an artificial satellite, others are awakened from their very sleep by cold and hunger.

*Donato G. Alarcon, M.D., F.C.C.P.**
Mexico D.F., Mexico

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*Regent for Mexico

The President's Page

A glimpse into the following pages should suffice to whet the appetite of any College member who has not already formulated plans to attend the 24th annual meeting in San Francisco from June 18 through 22, 1958. The outstanding scientific program which follows is indeed a tribute to the labors of the Committee on Scientific Program and the able leadership of co-chairmen, Drs. Peter A. Theodos and Samuel Bellet. The diligence of effort and intensiveness of thought which have gone into the planning of this program are attested to by the high calibre of material and speakers throughout this program.

It has been most gratifying to observe the manner in which the scientific programs of the College meetings have grown and diversified through the years in adaptation to the growth and consequent diversification of membership interests. The constant demand to keep pace is being met with an eye already cast well into the future.

The new horizons which now beckon to all mankind as we plunge even deeper into the jet age offer a particular challenge to the physician specializing in diseases of the chest. Taking full cognizance of the aroused interest in this new field, our program committee has included a panel on "The Jet Age and Chest Medicine" in which the role of the chest specialist in this new era is expanded upon.

It is evident that no effort has been spared in securing authorities of international repute as speakers and panelists to present and discuss a variety of topics tailored to the specific interests of our members. No member who looks over the program on these pages can fail to find numerous topics which fall within his own particular field of interest whatever it may be.

The same high standards and diversity obtain in the fireside conferences and luncheon meetings which promise the top flight attractions those who regularly attend our meetings have come to expect. Many members in the past have been disappointed in being unable to secure luncheon tickets for the round table discussions. Keen interest in these luncheons has resulted in an overwhelming demand for the limited space available. Therefore to avoid this disappointing experience, I urgently recommend to all members that they send in their luncheon reservations as early as possible.

The Committee on Scientific Program and co-chairmen, Drs. Theodos and Bellet, are deserving of our sincere thanks for a splendid achievement in preparing such a standout program for the meeting this year.

Every doctor recognizes the fact that the role of a member of the medical profession in society extends far beyond the field of medicine. The doctor of today is a citizen of the world and his influence is felt around the globe. Through attendance at meetings, reading journals, and correspondence, he engages in a constant exchange of information and ideas which contribute in many ways to the shaping of tomorrow's world. No issue today takes precedence over that of world peace. Recognizing our role in this vital issue, *Diseases of the Chest* has embarked on a series of editorials on the topic of "The Doctor and World Peace" written each month by members of the College in different parts of the world.

The "World Peace" editorial appearing in this issue is by Dr. Donato G. Alarcon, Regent, Mexico City. This editorial was chosen for publication in the April issue as part of our salute to Pan-American Week, April 13-19. The College has a deep interest in Latin America since among our 6000 members there are 895 members representing every country in this area.

In line with the global interests of the College, I wish to remind you of the Fifth International Congress on Diseases of the Chest, September 7-11, 1958 in Tokyo, Japan. I cannot urge you strongly enough to attend this outstanding Congress which, in addition to offering a superb scientific program, promises to be a truly memorable experience for all.

Burgess L. Gordon

24th ANNUAL MEETING
AMERICAN COLLEGE OF CHEST PHYSICIANS
FAIRMONT HOTEL, SAN FRANCISCO

SEMINARS

Wednesday, June 18

Morning Sessions—9:00 a.m.

AM-1 PULMONARY DISEASE (MEDICAL)

Chairman:

James Kieran, Clinical Instructor in Medicine, Stanford University, School of Medicine, San Francisco, California

9:00 A.M.—The Principles of Pulmonary Physiology As They Apply to Clinical Medicine
Robert B. Stonehill, Major USAF (MC), Chief, Pulmonary Disease Service, and Pulmonary Physiology Laboratory, 3700th USAF Hospital, Lackland Air Force Base, Texas

9:35 A.M.—Sarcoidosis
Marvin S. Harris, Clinical Professor of Thoracic Diseases, College of Medical Evangelists, Los Angeles, California

10:10 A.M.—Mucoviscidosis
Paul E. Wilson, Assistant Clinical Professor of Pediatrics, Stanford University, School of Medicine, San Francisco, California

10:45 A.M.—Trends in Allergic Diseases of the Chest
Ralph Bookman, Instructor in Medicine, University of Southern California, School of Medicine, Los Angeles, California

11:20 A.M.—Current Concepts in Coccidioidomycosis
William Winn, Medical Director, Tulare-Kings County Sanitarium, Springville, California

A ten-minute question and answer period will follow each lecture

AM-2 CARDIOLOGY (SURGICAL)

Chairman:

Sanford Leeds, Assistant Clinical Professor of Surgery, University of California, School of Medicine; Associate Chief of Surgery In Charge of Cardiac Surgery, Mt. Zion Hospital, San Francisco, California

9:00 A.M.—Physiologic Evaluation of Patients for Cardio-Vascular Surgery
Elliott Rappaport, Assistant Clinical Professor of Medicine, University of California, School of Medicine; Director, Cardio-Pulmonary Laboratory, Mt. Zion Hospital, San Francisco, California

9:35 A.M.—Surgical Treatment of Congenital Heart Disease
Benson Roe, Assistant Clinical Professor of Surgery, University of California, School of Medicine, San Francisco, California

10:10 A.M.—Surgical Treatment of Acquired Heart Disease
Elmer C. Rigby, Chairman, Cardio-Thoracic Surgery Section, Queen of Angels Hospital, Los Angeles, California

10:45 A.M.—Surgical Approach to Coronary Artery Disease
Alfred Goldman, Attending Thoracic Surgeon, Cedars of Lebanon Hospital, Los Angeles; Director, Thoracic and Cardiac Hospital, City of Hope Medical Center, Duarte, California

11:20 A.M.—Surgery of Extra-Cardiac Vascular Anomalies
Paul C. Samson, Associate Consultant in Thoracic Surgery, University of California, School of Medicine, San Francisco, California

A ten-minute question and answer period will follow each lecture

Please complete reservation form on page 466

Seminars (continued)

Afternoon Sessions—2:00 p.m.

PM-1 PULMONARY DISEASE (SURGICAL)

Chairman:

Thomas B. Wiper, M.D., Thoracic Surgeon, San Francisco, California

2:00 P.M.—*Bronchopulmonary Segmental Anatomy*

Ian W. Monie, Associate Professor of Anatomy, University of California, School of Medicine, San Francisco, California

2:35 P.M.—*Surgical Treatment of Bronchogenic Carcinoma*

H. B. Stephens, Associate Clinical Professor of Surgery, University of California, School of Medicine, San Francisco, California

3:10 P.M.—*Surgical Approach to Treatment of Emphysema; Physiologic Aspects*

Roger H. L. Wilson, Assistant Clinical Professor of Medicine, University of California, School of Medicine, San Francisco, California

3:45 P.M.—*Surgical Aspects in the Treatment of Emphysema*

Orville Grimes, Assistant Professor of Surgery, University of California, School of Medicine, San Francisco, California

4:20 P.M.—*Changing Trends in Surgical Treatment of Tuberculosis*

David J. Dugan, Clinical Instructor in Surgery, Stanford University, School of Medicine; Consultant in Thoracic Surgery, Oakland Veterans Administration Hospital, San Francisco, California

A ten-minute question and answer period will follow each lecture

PM-2 CARDIOLOGY (MEDICAL)

Chairman:

Eliot Corday, Assistant Clinical Professor of Medicine, University of California at Los Angeles; Chief, Cardiac Clinic, Cedars of Lebanon Hospital, Los Angeles

2:00 P.M.—*Evaluation and Treatment of Heart Disease in Children*

Sol Robinson, Associate Clinical Professor of Pediatrics, Stanford University, School of Medicine, San Francisco, California

2.35 P.M.—*Re-Evaluation of the Medical Treatment of Hypertension*

William H. Thomas, Assistant Clinical Professor of Medicine, University of California, School of Medicine, San Francisco, California

3:10 P.M.—*The Recognition of Minor Myocardial Infarctions*

John J. Sampson, Clinical Professor of Medicine, University of California, School of Medicine, San Francisco, California

3:45 P.M.—*Vectorcardiography—Clinical and Research Applications*

Herman N. Uhley, Assistant in Medicine, Research Associate, Harold Brunn Institute, Mt. Zion Hospital, San Francisco, California

4:20 P.M.—*Recognition and Treatment of Cor Pulmonale*

Edward C. Rosenow, Jr., Associate Clinical Professor of Medicine, University of Southern California, School of Medicine, Los Angeles, California

A ten-minute question and answer period will follow each lecture

NOTE: These seminars on diseases of the chest will be presented at the Fairmont Hotel on Wednesday, June 18, and are open to all physicians. The seminars have been accredited by the Board of Examiners for candidates for Fellowship in the College. The registration fee for each seminar, which consists of a series of five lectures, is $7.50.

Registration for the seminars must be made in advance and accompanied by the tuition fee; seating capacity is limited and reservations will be accepted in the order received. A coupon for this purpose will be found on page 466. Please indicate your preference by number.

Please complete reservation form on page 466

SCIENTIFIC PROGRAM

Thursday, June 19

8:00 p.m.—Scientific Session

Chairmen:

Burgess L. Gordon, President, Albuquerque, New Mexico
Donald R. McKay, President-Elect, Buffalo, New York

THIRD LOUIS MARK MEMORIAL LECTURE

The Individual Man and Medicine
John B. deC. M. Saunders, Dean, School of Medicine; Professor of Anatomy and Chairman of the Department, University of California School of Medicine, San Francisco, California

PANEL ON THE JET AGE AND CHEST MEDICINE

Moderator:

W. Randolph Lovelace, II, Head, Section of Surgery, Lovelace Clinic, and Director, Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico

Panel:

Mr. Stanley Lippert, Coordinator, Human Factors Group, Interiors Design Section, Santa Monica Engineering Department, Douglas Aircraft Company, Inc., Santa Monica, California

Ulrich C. Luft, Head, Department of Physiology, Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico

David G. Simons, Major USAF, Chief, Space Biology Branch, Aero Medical Field Laboratory, Air Force Missile Development Center, Holoman Air Force Base, New Mexico

Kenneth L. Stratton, Director, Medical Services Division, American Airlines, LaGuardia Airport Station, New York

Clayton S. White, Director of Research, Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico

Friday, June 20

9:00 a.m.—Scientific Session No. 1

Opening Remarks:

Peter A. Theodos, Philadelphia, Pennsylvania, Chairman, Section on Pulmonary Diseases, Committee on Scientific Program

Symposium on Tuberculosis (Medical and Surgical)

Varieties of Acid Fast Bacilli and Their Relationship to Disease in Man
Emil Bogen, Director of Laboratories and Research, and Seymour Froman, Microbiologist, Olive View Sanatorium, Olive View, California

The Role of the Cycloserine (Seromycin) Blood Level in the Treatment of Pulmonary Tuberculosis and the Prevention and Control of Cycloserine (Seromycin) Toxicity
George E. Martin, Medical Director, K. I. Fetterhoff, and C. X. Holmes, Pittsburgh State Tuberculosis Hospital, Pittsburgh, Pennsylvania

Massive Dose Isoniazid Therapy in Chronic Pulmonary Tuberculosis
J. J. Kirschner, Medical Director, Eagleville Sanatorium, Eagleville, Penna.

Continued Observations on the Role of Steroid Therapy in Tuberculosis
Annabel B. Miller, Chief, Pulmonary Disease Section, Veterans Administration Hospital, Buffalo, New York

Success in Repeat Treatment vs. Original Treatment of Tuberculosis
W. L. Howard, Superintendent, W. H. Maybury Sanatorium, Northville, Mich.

A Study of Primary Tuberculosis with Emphasis on the Intradermal Tuberculin Reaction Before and After Treatment
William B. Leftwich, Chief, Pulmonary Disease Service, Highland Alameda County Hospital, Oakland, California

Specific Tuberculin Sensitivity
Lydia B. Edwards, Medical Director, Tuberculosis Program, Division of Special Health Services, Department of Health, Education and Welfare, Washington

Comparative Morbidity and Mortality of Antimicrobially Treated and Untreated Idiopathic Effusion in the Negro
John H. Seabury, Professor of Medicine, John B. Bobear, Instructor in Medicine and M. Jack Liberman, Louisiana State University School of Medicine, New Orleans, Louisiana

Friday, June 20 (continued)

The Management and Chemotherapy of Tuberculosis in Pregnancy
Irving J. Selikoff, and Henry L. Dorfmann, Department of Medicine (Thoracic Division), The Mount Sinai Hospital, New York City

Current Status of Surgery in Pulmonary Tuberculosis (A summary report)
Lyman A. Brewer, III, Associate Professor of Surgery, College of Medical Evangelists, and Edward L. King, Attending Staff, Los Angeles County Hospital, Los Angeles, California

9:00 a.m.—Scientific Session No. 2

Opening Remarks:
Samuel Bellet, Philadelphia, Pennsylvania, Chairman, Section on Cardiovascular Diseases, Committee on Scientific Program

Symposium on Clinical Cardiology

Some Factors in the Pathogenesis of Atherosclerosis
David M. Spain, Associate Professor of Pathology, Columbia University College of Physicians and Surgeons, New York City; and Victoria B. Bradess, Director, Department of Laboratories and Research, Westchester County, Valhalla, N. Y.

Angina Pectoris Inversa and Heberden's Angina; Clinical and Experimental Observations
Myron Prinzmetal, Professor of Clinical Medicine, University of California School of Medicine, Los Angeles, California; Naci Bor, Research Fellow, Takashi Wada, Research Fellow, and Rexford Kennamer, Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, California

Factors in the Onset of Coronary Occlusion. Effort and Occupation
Arthur M. Master, Consultant Cardiologist, Mount Sinai Hospital, New York

The Clinical Use of Suprasternal Transaortic Coronary Arteriography
William Likoff, Associate Professor of Medicine, Joseph F. Uricchio, Associate in Medicine, William M. Lemmon, Resident in Thoracic Surgery and J. Stauffer Lehman, Professor and Head, Department of Radiology, Hahnemann Medical College, Philadelphia, Pennsylvania

Complete Relief of Mitral Stenosis by Neostrophingic Mobilization of the Obstructed Valve
Charles P. Bailey, Professor and Head, Department of Thoracic Surgery, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

Pulmonary Vascular Changes in Hypersensitivity States
George C. Griffith, Professor of Medicine (Cardiology), University of Southern California School of Medicine, Los Angeles, California

Chlorothiazide Therapy in Congestive Failure
Ralph V. Ford, Assistant Professor of Medicine and Pharmacology, Baylor University College of Medicine, Houston, Texas

12:00 noon—Round Table Luncheon Discussions (See page 454)

2:00 p.m.—Scientific Session No. 1

Forum on Basic Research in Diseases of the Chest: Pulmonary

Molar Sodium Lactate in Acute Adrenalin Fast Asthmatics
J. S. Blumenthal, Associate Clinical Professor of Medicine, E. B. Brown, Professor of Physiology, and G. S. Campbell, Assistant Professor of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota

An Evaluation of an Improved Rapid Method of Measuring Oxygen Tension
William F. Miller, Assistant Professor of Medicine, Brian J. Sproule, Research Fellow and Ivan E. Cushing, Resident, Internal Medicine, University of Texas Southwestern Medical School and Parkland Memorial Hospital, Dallas, Texas

Experimental Silicosis: The Inhibitory Effect of Iron
Paul Gross, Research Pathologist, Marian L. Westrick, Research Toxicologist and James M. McNerney, Assistant Research Toxicologist, Industrial Hygiene Foundation of America, Inc., Mellon Institute, Pittsburgh, Pennsylvania

The Biological Action of Inhaled Submicron Amorphous Silica Dusts
G. W. H. Schepers, Institute of Industrial Health and Department of Pathology, University of Michigan, Ann Arbor, Michigan

Changes of Stores of Carbon Dioxide During Voluntary Hyperventilation
John W. Vance, Fellow in Medicine and Ward S. Fowler, Section on Physiology, Mayo Clinic and Foundation, Rochester, Minnesota

SCIENTIFIC PROGRAM

Thursday, June 19

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Changes of Stores of Carbon Dioxide During Voluntary Hyperventilation
John W. Vance, Fellow in Medicine and Ward S. Fowler, Section on Physiology, Mayo Clinic and Foundation, Rochester, Minnesota

Friday, June 20 (continued)

Should A Chronic Atelectatic Lung Be Reaerated or Excised
John R. Benfield, Assistant Resident, Edwin T. Long, Resident Associate, Robert W. Harrison, Instructor, John F. Perkins, Jr., Associate Professor of Physiology, Gerald P. Herman, Intern, and William E. Adams, Raymond Professor of Surgery, University of Chicago School of Medicine, Chicago, Illinois

Fluoroscopic Pulmonary Densiography: Application to the Diagnosis of Chest Disease
Albert H. Andrews, Jr., Attending Bronchoesophagologist and Director, Respiration Laboratory, Robert J. Jensik, Attending Thoracic Surgeon, and William H. Pfisterer, Attending Radiologist, Presbyterian-St. Luke's Hospital, Chicago

Effect of Intermittent Positive Pressure Breathing on the Cardiac Output
Richard T. Cathcart, Assistant Professor of Medicine, William Fraimow, Fellow in Cardiopulmonary Research, Thomas Nealon, Instructor in Surgery, and Joyce Price, R.N., Jefferson Medical College, Philadelphia, Pennsylvania

2:00 p.m.—Scientific Session No. 2

Forum on Basic Research in Diseases of the Chest: Cardiac

Measurement of Thoracic Lymphatic Flow in Dogs by a New Method, With Its Clinical Implications
Herman N. Uhley, Assistant in Medicine, Sanford E. Leeds, Associate Chief of Surgery, John J. Sampson, Chief of Medicine, Mount Zion Hospital, and Meyer Friedman, Director, Harold Brunn Institute, Mount Zion Hospital, San Francisco, California

Newer Aspects of Diagnostic and Therapeutic Management of Acute Idiopathic Pericarditis
R. E. Fremont, Clinical Assistant Professor of Medicine, State University of New York Downstate Medical Center, Brooklyn, New York

Determinants of Pulmonary Blood Volume and Vascular Pressures
Peter F. Salisbury, Institute for Medical Research and Department of Medicine and Pierre-M. Galletti, Research Fellow, Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, California

Myocardial Revascularization by Cardiopneumopexy (185 Dogs and 21 Humans)
Franklin R. Smith, Clinical Associate in Surgery, University of Washington School of Medicine, Seattle, Washington

Left Heart Catheterization for the Evaluation of Mitral and Aortic Valvular Disease
William S. Blakemore, J. William White Assistant Professor of Surgical Research, Harrison Department of Surgical Research, H. M. Woske, Associate in Medicine, D. F. Heiman, Instructor in Medicine, B. Jumbala, Instructor in Medicine and Hadley Conn, Assistant Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Hemodynamic Response of Brain, Liver, Kidney and Coronary Circulation to Vasopressor Drugs
Eliot Corday, Assistant Clinical Professor of Medicine, John Williams, Research Fellow, Lauro B. de Vera, Research Fellow and Herbert Gold, Instructor in Medicine, University of California School of Medicine, Los Angeles, California

The Use of Extracorporeal Circulation in Cardiac Surgery
F. Henry Ellis, Jr., Head of a Surgical Section, and John W. Kirklin, Head of a Surgical Section, Mayo Clinic, Rochester, Minnesota

8:15 p.m.—Scientific Session

"Fireside Conferences"
Subjects and Discussion Leaders

Management of Pulmonary Emphysema
Alvan L. Barach, Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York City
Ward S. Fowler, Consultant in Physiology, Mayo Clinic, Rochester, Minnesota

Cancer of the Lung
L. Henry Garland, Clinical Professor of Radiology, Stanford University School of Medicine, San Francisco, California
Robert R. Shaw, Clinical Professor of Surgery, University of Texas Southwestern Medical School, Dallas, Texas

Fireside Conferences (continued)

Risk of Major Surgery in Cardiac Operation and Results of Aortic and Mitral Valve Surgery. Recent Advances

W. Donald Close, Associate Professor of Medicine, Indiana University School of Medicine, Indianapolis, Indiana
C. Walton Lillehei, Professor of Surgery, University of Minnesota Medical School and Variety Club Heart Hospital, Minneapolis, Minnesota

Electrocardiography. Vectorcardiography. Ballistocardiography.

George E. Burch, Henderson Professor and Chairman, Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana
Manuel Gardberg, Clinical Associate Professor of Medicine, Louisiana State University School of Medicine, New Orleans, Louisiana

Recent Developments in Tuberculin Testing

J. Arthur Myers, Professor of Medicine and Public Health, University of Minnesota Medical and Graduate Schools, Minneapolis, Minnesota
Julius B. Novak, Medical Director, Tuberculosis Institute of Chicago, Illinois

The Viruses in Respiratory Diseases

Milton V. Davis, Thoracic Surgeon, Dallas, Texas
Edwin H. Lennette, Chief, Viral and Rickettsial Disease Laboratory, California State Department of Public Health, Berkeley, California
Thomas G. Ward, Professor of Virology, University of Notre Dame, Notre Dame, Indiana

Anticoagulant Therapy

Lawrence R. Coke, Assistant Professor of Medicine, University of Manitoba, Winnipeg, Manitoba
Benjamin Manchester, Assistant Clinical Professor of Medicine, George Washington University School of Medicine, Washington, D. C.

Immunization in Tuberculosis

Lewis S. Jordan, Superintendent and Medical Director, Riverside Sanatorium, Granite Falls, Minnesota
Sol Roy Rosenthal, Medical Director, Research Foundation, Chicago, Illinois

Esophageal Disease

Roy G. Klepser, Associate Professor of Thoracic Surgery, Georgetown University Medical School, Washington, D. C.
Herman J. Moersch, Chairman, Section of Internal Medicine, Mayo Clinic, Rochester, Minnesota
Elmer C. Rigby, Active Staff, St. Vincent's Hospital, Los Angeles, California

Cor Pulmonale

George R. Herrmann, Professor of Medicine, University of Texas Medical Branch, Galveston, Texas
Irving Mack, Associate Attending Physician, Chest Department, Michael Reese Hospital, Chicago, Illinois

The Use of Inhalation Therapy

Edwin R. Levine, Assistant Professor of Clinical Medicine, Chicago Medical School, Chicago, Illinois
Theodore H. Noehren, Assistant Professor of Internal Medicine, University of Buffalo College of Medicine and the Buffalo General Hospital, Buffalo, New York
Max S. Sadove, Division of Anesthesiology, University of Illinois Research and Educational Hospitals, Chicago, Illinois

The Chest Physician In Court

Mr. Edward D. Bronson, Attorney-at-law, San Francisco, California
Mr. John Wynne Herron, Trial Attorney, San Francisco, California
Joseph F. Sadusk, Jr., Member, Committee on Medico-Legal Problems, American Medical Association; Associate Clinical Professor of Medicine, Stanford University School of Medicine, San Francisco, California

Coronary Disease Including Medical and Surgical Therapy

B. L. Brofman, Director, Cardiovascular Research, Mount Sinai Hospital, Cleveland, Ohio
Johann L. Ehrenhaft, Professor of Surgery, Chairman, Division of Thoracic Surgery, State University of Iowa, Iowa City, Iowa
Joseph Edeiken, Assistant Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Pulmonary Aspects of Collagen Diseases

Benson Bloom, Assistant Director of Professional Services, Veterans Administration Hospital, Bronx, N. Y.
O. J. Farness, Private practice, Diseases of the Chest, Tucson, Arizona

Fireside Conferences (continued)

Fungus Diseases of the Chest

Michael L. Furcolow, Medical Director, Public Health Service, Kansas City, Kans.
B. H. Webster, Visiting Physician, Department of Chest and Internal Medicine, St. Thomas Hospital, Nashville, Tennessee

Rheumatic and Congenital Heart Disease—Therapy and Prophylaxis

Benjamin M. Gasul, Director, Pediatric Cardiophysiology Department, Cook County Children's Hospital, Chicago, Illinois
Richard D. Rowe, Assistant Physician, Hospital for Sick Children, Toronto

The Practical Evaluation of Lung Function

S. Thatcher Hubbard, Jr., Director, Cardio-Respiratory Laboratory (Private), Spokane, Washington
Ross C. Kory, Associate Professor of Medicine, Marquette University School of Medicine, Milwaukee, Wisconsin

Sarcoidosis

Martin M. Cummings, Director, Research Service, Veterans Administration, Washington, D. C.
Edward Lebovitz, Instructor of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
David Salkin, Director, Professional Services, Veterans Administration Hospital, San Fernando, California

Resuscitation of Heart—Treatment of Cardiac Arrest

Thomas G. Baffes, Assistant Attending Surgeon, Children's Memorial Hospital, Chicago, Illinois
E. Sterling Nichol, formerly Medical Director, Miami Heart Institute, Miami Beach, Florida
J. Karl Poppe, Clinical Associate, Department of Surgery, University of Oregon Medical School, Portland, Oregon

The Use and Abuse of Steroid Therapy in Pulmonary Disease

Winthrop N. Davey, Associate Professor in Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan
David B. Radner, Director, Chest Department, Michael Reese Hospital, Chicago

Biopsy Procedures in Chest Diseases

Albert C. Daniels, Clinical Assistant Professor of Surgery, Stanford University School of Medicine, San Francisco, California
Karl P. Klassen, Chief of the Thoracic Surgery Service, Ohio State University Health Center, Columbus, Ohio

Hypertension

Thomas J. Coogan, Associate in Medicine, University of Illinois College of Medicine, Chicago, Illinois
Milton Mendlowitz, Associate Attending Physician, Mount Sinai Hospital, New York City

Allergy in Pulmonary Disease

Leon Unger, Associate Professor of Medicine, Northwestern University Medical School, Chicago, Illinois
Orval R. Withers, Associate Clinical Professor of Medicine, University of Kansas School of Medicine, Kansas City, Missouri

Arrhythmias

Louis F. Bishop, Assistant Clinical Professor of Medicine, New York University College of Medicine, New York City
Arthur E. Lamb, Clinical Associate Professor of Medicine, State University of New York College of Medicine, New York City

Management of Chest Injuries

David P. Boyd, Thoracic Surgeon, Lahey Clinic, Boston, Massachusetts
Emil A. Naclerio, Chief, Thoracic Surgery, Harlem Hospital, New York

Treatment of Tuberculosis in Infants and Children

Lloyd B. Dickey, Professor of Pediatrics, Stanford University School of Medicine, San Francisco, California
Katherine H. K. Hsu, Assistant Professor of Pediatrics, Baylor University College of Medicine, Houston, Texas

Trauma in Heart Disease. Medico-Legal Aspects of Cardiovascular Disease

Mr. Edmund J. Thomas, Secretary-Presiding Referee, Industrial Accident Commission, San Francisco, California
Henry J. Stanford, Consultant Thoracic Surgeon, Veterans Administration Hospital, Tucson, Arizona

Fireside Conferences (continued)

New Trends in Physical Rehabilitation of Cardio-Pulmonary Disease

John H. Aldes, Director, Rehabilitation Center, Cedars of Lebanon Hospital, Los Angeles, California

Edward A. Piszczek, Field Director, The Suburban Cook County Tuberculosis Sanitarium District, Forest Park, Illinois

Saturday, June 21

10:00 a.m.—Combined Scientific Session

Pulmonary and Cardiac Function Studies in Sickle Cell Lung Disease

Kenneth M. Moser, Assistant Chief, Peter C. Luchsinger, Chief, Cardiopulmonary Laboratory, District of Columbia General Hospital, Washington, D. C., and Sol Katz, Adjunct Clinical Professor of Medicine, Georgetown and George Washington University Medical Schools, Washington, D. C.

Bronchogenic Cysts in Patients Presumed to Have Pulmonary Tuberculosis

Neil C. Andrews, Chief of Surgery, Philip C. Pratt, Chief of Laboratories and A. J. Christoforidis, Chief of Radiology, Ohio Tuberculosis Hospital, Columbus, Ohio

Forum on Pulmonary and Cardiovascular Effects of Smoking

Moderator:

Julius H. Comroe, Director, Cardiovascular Research Institute, University of California Medical Center, San Francisco, California

Panel:

Kelly T. McKee, Associate Professor of Medicine, Medical College of South Carolina, Charleston, South Carolina

McKeen Cattell, Professor of Clinical Pharmacology, Cornell University Medical College, New York City

Richard J. Bing, Professor of Medicine, Washington University School of Medicine, St. Louis, Missouri

12:00 noon—Round Table Luncheon Discussions (See page 455)

2:00 p.m.—Scientific Session No. 1

Implications of Recent Findings on the Pathology and Pathogenesis of Benign Pulmonary Histoplasmosis

Henry C. Sweany, Director of Research and Pathology, David F. Gorelick, Consulting Pathologist, Fred C. Coller, Consulting Pathologist and James L. Jones, Histological Technician, Missouri State Sanatorium, Mount Vernon, Missouri

Middle Lobe Disease

David H. Waterman, Sheldon E. Domm and William K. Rogers, Attending Thoracic Surgeons, University of Tennessee Memorial Research Center and Hospital, Knoxville, Tennessee

Trigger Mechanisms in Asthma

Richard H. Overholt, Thoracic Surgeon, New England Deaconess and New England Baptist Hospitals, Boston, Massachusetts

Symposium on Idiopathic Interstitial Fibrosis of the Lung

Moderator:

H. Corwin Hinshaw, Clinical Professor of Medicine (Diseases of the Chest), Stanford University School of Medicine, San Francisco, California

Panel:

Hurley L. Motley, Professor of Medicine and Director, Cardio-Respiratory Laboratory, University of Southern California, Los Angeles, California

David M. Spain, Associate Professor of Pathology, Columbia University College of Physicians and Surgeons, New York City

Gary Zucker, Assistant Clinical Professor of Medicine, New York University College of Medicine, New York City

2:00 p.m.—Scientific Session No. 2

Coronary Arteriography

Charles T. Dotter, Professor of Radiology, Louis H. Frische, Associate Professor of Radiology, Etsuko Kawashima, Resident in Radiology, and W. Hoskinson, Medical Student, University of Oregon Medical School, Portland, Oregon

Intracardiac Surgery Using the Kay-Anderson Heart Lung Machine

Jerome Harold Kay, Robert M. Anderson, Louis C. Bennett, Rubin Lewis, William Musicant, Edward M. Synder, Jr., John Meihaus, Oscar Magidson and Jack Sheinkopf, University of Southern California School of Medicine and St. Vincent's Hospital, Los Angeles, California

Saturday, June 21 (continued)

The Use of Myocardial Electrode Inserted Percutaneously for Control of Complete Atrial Ventricular Block by an Artificial Pacemaker
C. Walton Lillehei, Professor of Surgery, Andre Thenet and Paul Hodges, University of Minnesota Medical School and Variety Club Heart Hospital, Minneapolis, Minnesota

Surgery in Mitral Stenosis—(The report of the Section on Cardiovascular Surgery of the Committee on Cardiovascular Disease)
Charles P. Bailey, Professor and Head, Department of Thoracic Surgery, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

Panel on Atherosclerosis

Moderator:
William Likoff, Associate Professor of Medicine, Hahnemann Medical College, Philadelphia, Pennsylvania

Panel:
George E. Burch, Henderson Professor and Chairman, Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana
Stephen R. Elek, Associate Clinical Professor of Medicine, University of Southern California School of Medicine, Los Angeles, California
Maurice Sokolow, Associate Professor of Medicine, Chief of Cardiovascular Division, Department of Medicine, University of California School of Medicine, San Francisco, California

Sunday, June 22

9:00 a.m.—Scientific Session No. 1

Symposium on the Biologic Effects of Radio-Active Exposure on the Lungs

Moderator:
L. Henry Garland, Clinical Professor of Radiology, Stanford University School of Medicine, San Francisco, California

Panel:
Hardin B. Jones, Professor of Physiology, University of California School of Medicine, San Francisco, California
George R. Meneely, Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee
Sydney F. Thomas, Assistant Clinical Professor of Radiology, Stanford University School of Medicine, San Francisco, California

Symposium on the Biologic Effects of Air Pollution on the Lungs

Moderator:
Seymour M. Farber, Associate Clinical Professor of Medicine, In Charge, University of California Tuberculosis and Chest Service, San Francisco, California

Panel:
John R. Goldsmith, Head, Studies of Health Effects of Air Pollution, California Department of Public Health, Berkeley, California
Albert Roberts, Chief, Clinical Investigation, Air Pollution Medical Program, Public Health Service, Wahsington, D. C.
Moyer D. Thomas (D.Sc.), Stanford Research Institute, Menlo Park, Cal.

9:00 a.m.—Scientific Session No. 2

Clinical Cardiac Conference

Moderator:
John J. Sampson, Clinical Professor of Medicine, University of California School of Medicine, San Francisco, California

Panel:
Jesse L. Carr, Clinical Professor of Pathology, University of California School of Medicine, San Francisco, California
Eliot Corday, Assistant Clinical Professor of Medicine, University of California School of Medicine, Los Angeles, California
Earle B. Kay, Director of Cardiovascular Surgery, St. Vincent's Charity Hospital, Cleveland, Ohio
Arthur M. Master, Consultant Cardiologist, The Mount Sinai Hospital, New York City
Arthur Selzer, Clinical Professor of Medicine, Stanford University School of Medicine, San Francisco, California

Sunday, June 22 (continued)

Symposium on Congenital Heart Disease

Moderator:

Saul J. Robinson, Associate Clinical Professor of Pediatrics, Stanford University School of Medicine, Chief of Pediatrics, Mount Zion Hospital, San Francisco, California

The Pathologic Anatomy of Ventricular Septal Defects

Maurice Lev, Director, Congenital Heart Disease Research and Training Center, Hektoen Institute, Chicago, Illinois

Follow-Up Studies on the Hemodynamics of Ventricular Septal Defects

Joshua Lynfield, Associate in Cardiophysiology, Cook County Hospital, Chicago, Illinois

Clinical Findings in Patients with Ventricular Septal Defects

James DuShane, Assistant Professor of Pediatrics, University of Minnesota Graduate School of Medicine, Rochester, Minnesota

Present Day Views Regarding Surgery in Patients with Ventricular Septal Defects

Denton A. Cooley, Associate Professor of Surgery, and Dan G. McNamara, Associate Professor of Pediatrics, Baylor University College of Medicine, Houston, Texas

PANEL DISCUSSION

Moderator:

Saul J. Robinson, San Francisco, California

Panel:

Denton A. Cooley, Houston, Texas
James DuShane, Rochester, Minnesota
Maurice Lev, Chicago, Illinois
Joshua Lynfield, Chicago, Illinois

12:00 noon—Round Table Luncheon Discussions (See page 456)

2:00 p.m.—Combined Scientific Session

Clinical and Roentgenologic Signs of Collagen Diseases Involving the Thorax

Charles M. Nice, Jr., Associate Professor of Radiology, University of Minnesota Medical School, Minneapolis, Minnesota; A. N. K. Menon, Lecturer in Radiology, Stanley Medical College, Madras, India, and Leo G. Rigler, Director of Postgraduate Medical Education, Cedars of Lebanon Hospital, Los Angeles, California

Myasthenia and Malignant Intrathoracic Tumors

Edward H. Lambert, Associate Professor of Physiology, E. Douglas Rooke, Instructor in Neurology, Lee M. Eaton, Professor of Neurology, and Corrin H. Hodgson, Assistant Professor of Medicine, Mayo Foundation Graduate School, University of Minnesota, Minneapolis, Minnesota

Primary Pulmonary Hypertension

Harry Goldberg, Assistant Professor of Medicine, Jonas Brachfeld, Former Cardiac Fellow, and Attilio Reale, Former Cardiac Fellow, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

The Prognosis of Lung Cancer

Katharine R. Boucot, Professor of Preventive Medicine and Clinical Professor of Medicine, Utako Horie, Lois Mattox Miller Fellow in Preventive Medicine, Woman's Medical College of Pennsylvania; and Martin J. Sokoloff, Associate Professor of Medicine, Jefferson Medical College, Philadelphia, Pennsylvania

Evolution of Carcinoma of the Lung

Leo G. Rigler, Director of Postgraduate Medical Education, Cedars of Lebanon Hospital, Los Angeles, California

Post Traumatic Aneurysm of the Thoracic Aorta

James C. Hunt, Section of Medicine, Howard B. Burchell, and F. Henry Ellis, Section of Surgery, Mayo Clinic, Rochester, Minnesota

Esophageal Replacement with a Reversed Gastric Tube

Henry J. Heimlich, Adjunct Thoracic Surgeon, Montefiore Hospital, New York City

Intracardiac Anatomy in Patients with Congenital Heart Lesions

F. Mason Sones, Jr., Director, Cardiac Catheterization Laboratory, Cleveland Clinic Foundation, Cleveland, Ohio

ROUND TABLE LUNCHEONS

Friday, June 20

A-1 ***Recent Advances in Diagnosis and Therapy of Coronary Disease***

Richard A. Gilman, Thoracic and Cardiovascular Surgeon, San Diego, California

Lewis Gunther, Co-Chief of Medicine, Cedars of Lebanon Hospital, Los Angeles, California

Nathaniel E. Reich, Clinical Assistant Professor of Medicine, State University of New York College of Medicine, Brooklyn, New York

Moderator: Oglesby Paul, Clinical Associate Professor of Medicine, University of Illinois College of Medicine, Chief of Cardiac Clinic and Assistant Attending Physician, Presbyterian Hospital, Chicago, Illinois

A-2 ***Cardiac in Industry***

Daniel C. Braun, Lecturer in Occupational Medicine, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania

Samuel A. Weisman, Associate Clinical Professor of Medicine, University of Southern California School of Medicine, Los Angeles, California

Paul J. Whitaker, Medical Director, Allis-Chalmers Manufacturing Company, West Allis, Wisconsin

Moderator: John F. Briggs, Associate Professor of Clinical Medicine, University of Minnesota, Minneapolis, Minnesota

A-3 ***Treatment of the Patient with Inoperable Lung Cancer***

William F. Mazzitello, Assistant Professor of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota

John P. Medelman, Clinical Associate Professor of Radiology, University of Minnesota Medical School, Minneapolis, Minnesota

Richard H. Overholt, Thoracic Surgeon, New England Deaconess Hospital, Boston, Massachusetts

Moderator: William E. Adams, Raymond Professor of Surgery, University of Chicago School of Medicine, Chicago, Illinois

A-4 ***Management of Chronic Respiratory Insufficiency***

Howard G. Dayman, Assistant Professor of Medicine, University of Buffalo School of Medicine, Buffalo, New York

Marvin S. Harris, Clinical Professor of Thoracic Diseases, College of Medical Evangelists, Los Angeles, California

William Lees, Chief of Surgery, Municipal Tuberculosis Sanatorium, Associate Clinical Professor in Surgery, Stritch School of Medicine of Loyola University, Chicago, Illinois

Moderator: Maurice S. Segal, Clinical Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts

A-5 ***Management of the Tuberculous Patient Unresponsive to the Usual Methods of Treatment***

Sumner S. Cohen, Assistant Medical Director, Glen Lake Sanatorium, Oak Terrace, Minnesota

Roger S. Mitchell, Associate Professor of Medicine, University of Colorado School of Medicine, Denver, Colorado

James A. Wier, Col., Chief, Pulmonary Disease Service, Fitzsimons Army Hospital, Denver, Colorado

Moderator: Karl H. Pfuetze, Medical Director and Superintendent, Chicago State Tuberculosis Sanatorium, Chicago, Illinois

A-6 ***Newer Antibiotic Therapy of Non-Tuberculous Infections of the Respiratory Tract***

Joseph E. Geraci, Assistant Professor of Medicine, Mayo Clinic and University of Minnesota Graduate School of Medicine, Rochester, Minnesota

Alfred Goldman, Associate Professor of Clinical Medicine, Washington University School of Medicine, St. Louis, Missouri

William M. M. Kirby, Professor of Medicine, University of Washington Medical School, Seattle, Washington

Moderator: Robert I. Wise, Assistant Professor of Medicine, Jefferson Medical College, Philadelphia, Pennsylvania

Please complete reservation form on page 466

ROUND TABLE LUNCHEONS

Saturday, June 21

B-1 ***Selection of Patients for Surgery with Acquired Valvular Lesions***

Robert P. Glover, Director of Cardiovascular Research Laboratories and Chief of Thoracic and Cardiac Surgery, Presbyterian Hospital, Philadelphia, Pennsylvania

Alfred Goldman, Director, Cardiac Hospital, City of Hope Medical Center, Duarte, California

Henry A. Zimmerman, Chief of Cardiovascular Service, St. Vincent's Charity Hospital, Cleveland, Ohio

Moderator: Arthur Selzer, Clinical Professor of Medicine, Stanford University School of Medicine, San Francisco, California

B-2 ***Trauma and Heart Disease (Rehabilitation)***

Ray W. Kissane, Professor of Medicine in Cardiology, Ohio State University College of Medicine, Columbus, Ohio

H. Easton McMahon, Assistant Clinical Professor of Medicine, New York Medical College, New York City

Joseph M. Ryan, Clinical Assistant Professor of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota

Moderator: Philip Lee, Department of Medicine, Palo Alto Medical Clinic, Palo Alto, California

B-3 ***Present Indications for Thoracic Surgical Procedures***

E. C. Drash, Clinical Professor of Surgery, University of Virginia School of Medicine, Charlottesville, Virginia

John B. Grow, Chief, Thoracic Surgery, National Jewish Hospital, Denver, Colorado

W. Elliott Harrison, Clinical Assistant Professor of Surgery, University of British Columbia, Vancouver, British Columbia

Moderator: Paul C. Samson, Associate Clinical Professor of Surgery, Stanford University School of Medicine, San Francisco, California

B-4 ***Pulmonary Embolism***

Chilton Crane, Senior Associate in Surgery, Peter Bent Brigham Hospital, Boston, Massachusetts

Ivan F. Duff, Associate Professor of Internal Medicine in Charge of Rackham Arthritis Research Unit, University of Michigan, Ann Arbor, Michigan

Travis Winsor, Assistant Clinical Professor of Medicine, University of Southern California School of Medicine, Los Angeles, California

Moderator: Harold L. Israel, Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

B-5 ***Problems in the Early Diagnosis of Pulmonary Emphysema***

J. K. Curtis, Clinical Professor of Medicine, University of Wisconsin Medical School, Madison, Wisconsin

Harold A. Lyons, Associate Professor of Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York

Bernard J. O'Loughlin, Associate Professor of Radiology, University of California School of Medicine, Los Angeles, California

Moderator: R. Drew Miller, Assistant Professor of Medicine, University of Minnesota Graduate Medical School, Rochester, Minnesota

B-6 ***The Evaluation of Disability in Industrial Lung Diseases***

Mr. Warren L. Hanna, Attorney-at-law, San Francisco, California

Abraham H. Russakoff, Associate Clinical Professor of Medicine, Medical College of Alabama, Birmingham, Alabama

Joseph F. Tomashefski, Assistant Professor of Medicine and Physiology, Ohio State University College of Medicine, Columbus, Ohio

Mr. Theodore C. Waters, Attorney-at-law, Baltimore, Maryland

Moderator: Reginald H. Smart, Clinical Professor of Medicine and Coordinator of Chest Disease Instruction, University of Southern California School of Medicine, Los Angeles, California

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ROUND TABLE LUNCHEONS

Sunday, June 22

C-1 ***Recent Advances in Cardiac Therapy***

Milton W. Anderson, Consultant in Medicine, Mayo Clinic, Rochester, Minnesota

John M. Askey, Associate Clinical Professor of Medicine, University of Southern California School of Medicine, Los Angeles, California

Benjamin Manchester, Assistant Clinical Professor of Medicine, George Washington University School of Medicine, Washington, D. C.

Moderator: John J. Sampson, Clinical Professor of Medicine, University of California School of Medicine, San Francisco, California

C-2 ***Congenital Malformations of the Heart***

Paul Adams, Jr., Assistant Professor of Pediatrics, University of Minnesota Medical School, Minneapolis, Minnesota

Robert A. Miller, Head Cardiologist, Children's Memorial Hospital, Chicago, Illinois

Morse Shapiro, Senior Cardiac Consultant, City of Hope Medical Center, Duarte, California

Moderator: Forrest Adams, Associate Professor of Pediatrics (Cardiology) University of California School of Medicine, Los Angeles, California

C-3 ***Problems in the Selection of Patients for Travel by Air—Present and Future***

Earl T. Carter, Assistant Professor of Preventive Medicine and Physiology, Ohio State University College of Medicine, Columbus, Ohio

Ross C. Kory, Associate Professor of Medicine, Marquette University School of Medicine, Milwaukee, Wisconsin

Ludwig G. Lederer, Chairman, Medical Committee, Air Transport Association of America, Washington, D. C.

Moderator: Roger H. L. Wilson, Assistant Clinical Professor of Medicine, University of California School of Medicine, San Francisco, California

C-4 ***Physiologic Treatment of Pulmonary Disease in Children***

John E. Affeldt, Medical Director, Rancho Los Amigos Respiratory Center for Polio, Hondo, California

Gordon E. Gibbs, Professor and Chairman, Department of Pediatrics, University of Nebraska College of Medicine, Omaha, Nebraska

Allan Hurst, Assistant Professor of Medicine, University of Colorado School of Medicine, Denver, Colorado

Moderator: Roy F. Goddard, Director, Pediatric Research Department, Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico

C-5 ***Pulmonary Manifestations of Cardiac Disease***

Arnold S. Anderson, Private practice, Diseases of the Chest, St. Petersburg, Florida

John S. LaDue, Associate Professor of Medicine, Cornell University Medical College, New York City

Paul C. Swenson, formerly Professor of Radiology, Jefferson Medical College, Philadelphia, Pennsylvania

Moderator: Corrin H. Hodgson, Consultant in Internal Medicine, Mayo Clinic, Rochester, Minnesota

C-6 ***The Management of Pulmonary Disease in Geriatric Patients***

Duane M. Carr, Professor of Surgery, University of Tennessee College of Medicine, Memphis, Tennessee

Alexander Libow, Associate Attending, Mount Sinai Hospital, Miami Beach, Florida

Joseph A. Smith, Medical Director, New Jersey Sanatorium for Chest Diseases, Glen Gardner, New Jersey

Moderator: Edward Kupka, Chief, Bureau of Tuberculosis, California State Department of Public Health, Berkeley, California

Please complete reservation form on page 466

SPECIAL EVENTS

Wednesday, June 18

3:30 p.m.—SEMINAR, COUNCIL AND COMMITTEE ON UNDERGRADUATE MEDICAL EDUCATION

Undergraduate Teaching of Tuberculosis and Chest Diseases at the University of California School of Medicine

Moderator: Seymour M. Farber, In Charge, University of California Tuberculosis and Chest Service, San Francisco, California

Differential Diagnosis

Alvin S. Hambly, Assistant Clinical Professor of Medicine, University of California School of Medicine, San Francisco, California

Antimicrobial Therapy

William Mandel, Clinical Instructor in Medicine, University of California School of Medicine, San Francisco, California

Pulmonary Physiology

Roger H. L. Wilson, Assistant Clinical Professor of Medicine, University of California School of Medicine, San Francisco, California

Cancer Cytology

Sam Pfarr, Senior Cytology Technician, University of California School of Medicine, San Francisco, California

Thoracic Surgery

Max E. Childress, Clinical Instructor in Surgery, University of California School of Medicine, San Francisco, California

Summarization

Mortimer A. Benioff, Assistant Clinical Professor of Medicine, University of California School of Medicine, San Francisco, California

Discussion

Theodore H. Noehren, Buffalo, New York
Chairman, Council on Undergraduate Medical Education
William M. Lees, Chicago, Illinois
Chairman, Committee on Undergraduate Medical Education

Thursday, June 19

4:00 p.m.—OPEN FORUM, COUNCIL ON HOSPITALS

Have We Exhausted Our Case-Finding in Chest Disease?

Chairman: Otto L. Bettag, Director, Illinois Department of Public Welfare, Chicago

Communities

Edward T. Blomquist, Medical Director, Chief, Tuberculosis Program, Division of Special Health Services, Department of Health, Education, and Welfare, Public Health Service, Washington, D. C.

Penal Institutions

John H. Fountain, Director, Division of Tuberculosis Control, King County Health Department, Seattle, Washington

General Hospitals

John P. Medelman, Clinical Associate Professor of Radiology, University of Minnesota Medical School, Minneapolis, Minnesota

Schools

J. Arthur Myers, Professor of Internal Medicine and Public Health, Medical and Graduate Schools, University of Minnesota, Minneapolis, Minnesota

Mental Institutions

Ernest Teller, Chief, Tuberculosis Control Service, Illinois Department of Public Welfare, Chicago, Illinois

Questions and discussion from the floor

4:00 p.m.—OPEN FORUM, COUNCIL ON RESEARCH

Alvan L. Barach, New York City, Chairman, Council on Research, presiding

Presentation of Committee Reports

The above meetings are open to all members of the College. Discussion from the floor.

ADMINISTRATIVE SESSIONS

Wednesday, June 18

8:00 a.m.—Committee on Seminars

10:00 a.m.—Executive Council

2:00 p.m.—Board of Regents

Thursday, June 19

9:00 a.m.—Meetings of all Councils and Committees

9:00 a.m.—Examinations for Fellowship (written)

12:00 noon—LUNCHEON, JOINT MEETING

Board of Governors and Boards of Regents

David H. Waterman, Knoxville, Tennessee, Chairman, Board of Governors, presiding

Awarding of Certificates of Merit to Past-Presidents of College Chapters

Burgess L. Gordon, Albuquerque, New Mexico, President

Presentation of Reports

Council on Undergraduate Medical Education
Theodore H. Noehren, Buffalo, New York, Chairman
Council on Postgraduate Medical Education
J. Winthrop Peabody Sr., Washington, D. C., Chairman
Council on Research
Alvan L. Barach, New York, N. Y., Chairman
Council on Hospitals
Otto L. Bettag, Chicago, Illinois, Chairman
Committee on Membership
Chevalier L. Jackson, Philadelphia, Pennsylvania, Chairman
Committee on Motion Pictures
Paul H. Holinger, Chicago, Illinois, Chairman
Committee on Liaison with State and County Medical Societies
Robert B. Morrison, Austin, Texas, Chairman
Committee on College Essay Contest
H. Allan Novack, Boston, Massachusetts, Chairman
College Books
Burgess L. Gordon, Albuquerque, New Mexico
Fifth International Congress on Diseases of the Chest
Tokyo, Japan, September 7-11, 1958
Murray Kornfeld, Chicago, Illinois
Silver Anniversary, 25th Annual Meeting
Atlantic City, June 3-7, 1959
Jay Arthur Myers, Minneapolis, Minnesota
Silver Anniversary, Homecoming Meeting
Albuquerque, New Mexico, 1959
Roy F. Goddard, Albuquerque, New Mexico
Silver Anniversary, Interim Session
Dallas, Texas, November 29-30, 1959
Alvis E. Greer, Houston, Texas

1:30 p.m.—Meeting, Oral Examiners

2:00 p.m.—Examinations for Fellowship (oral)

2:00 p.m.—Meetings of Council and Committee Chairmen

2:30 p.m.—Joint Meeting, Committee on Membership and College Chapter Officials

Friday, June 20

2:00 p.m.—Committee on Nominations

2:00 p.m.—Committee on Insurance

3:00 p.m.—Editorial Board

5:00 p.m.—Chapter Meetings

Saturday, June 21

9:00 a.m.—OPEN ADMINISTRATIVE SESSION
Burgess L. Gordon, Albuquerque, New Mexico, President, presiding
Report of the Historian
Report of the Treasurer
Report of the Executive Director
Report of the Committee on Nominations
Election of Officers

10:00 a.m.—Executive Council

Sunday, June 22

8:00 a.m.—Past-Presidents' Breakfast

10:00 a.m.—Executive Council

2:30 p.m.—Board of Regents

5:00 p.m.—Dinner Meeting, Section on Pediatric Cardiology
Benjamin M. Gasul, Chicago, Illinois, Chairman, presiding

SOCIAL ACTIVITIES

Saturday, June 21

6:00 p.m.—Annual Convocation (Formal)

7:00 p.m.—Cocktail Party
Sponsored by The Panray Corp., New York City

7:30 p.m.—Annual Presidents' Banquet
This is strictly a social evening and there will be no speeches

9:30 p.m.—After-Dinner Dancing
Sponsored by the California Chapter of the College. Music by the Jimmy Blass Orchestra

The above functions will be held at the Fairmont Hotel

LADIES ACTIVITIES

Thursday, June 19

12:30 p.m.—Luncheon, Piro's Restaurant
Within pleasant walking distance of delightful Jackson Square in one of the oldest sections of San Francisco. The Interior Decorator Display Shops will have open house with conducted tours especially for the ladies of the College.

Friday, June 20

6:30 p.m.—Cocktails

7:00 p.m.—Oriental Dinner, Terrace Room, Fairmont Hotel
Dinner will be followed by a Japanese Fashion Show including an enticing combination of costumes designed for modern leisure wear in Japanese fabrics and authentic Japanese Kimonos.

Saturday, June 21

6:00 p.m.—College Convocation

7:00 p.m.—Cocktail Party
Sponsored by The Panray Corp., New York City

7:30 p.m.—Annual Presidents' Banquet
This is a social event — no speeches

9:30 p.m.—After-Dinner Dancing
Sponsored by the California Chapter of the College. Music by the Jimmy Blass Orchestra

The Saturday functions will be held at the Fairmont Hotel

Sunday, June 22

Information brochures will be available at the Ladies Registration Desk and the members of the Ladies Reception Committee will be pleased to assist in arrangements for shopping, tours of Chinatown, Fisherman's Wharf, and other places of interest.

MOTION PICTURE PROGRAM

The following is a tentative program of films dealing with diseases of the chest which will be shown concurrently with the scientific program on Friday, Saturday and Sunday, June 20, 21 and 22. Additional films are being considered by the Committee on Motion Pictures of the College for presentation.

Differential Diagnosis and Treatment of Lobar Emphysema of Infants
Osler A. Abbott, Emory University School of Medicine, Emory University, Georgia

Traumatic Hernia of the Diaphragm
William E. Adams, John Todd Reynolds and Peter V. Moulder, University of Chicago and University of Illinois, Chicago, Illinois

Transposition of the Great Vessels
Thomas G. Baffes and Willis J. Potts, Children's Memorial Hospital, Chicago, Ill.

Segmental Resections of Multiple Congenital Arteriovenous Aneurysms
O. Theron Clagett, Mayo Clinic, Rochester, Minnesota

Surgical Removal Myxoma Left Auricle Simulating Mitral Stenosis
Denton A. Cooley and Joseph R. Latson, Baylor University College of Medicine, Houston, Texas

Repair of Interatrial Septal Defect Utilizing Cardiopulmonary By-Pass
Philip Crastnopol, Alvin A. Bakst, H. Gianfrancesco, E. A. Braunstein and Irving G. Kroop, Jewish Hospital and Jewish Chronic Disease Hospital, Brooklyn, New York

Closure of Interventricular Septal Defect Using the Pump Oxygenator
J. L. Ehrenhaft, State University of Iowa Hospitals, Iowa City, Iowa

Surgical Management of the Complications of Reflux Esophagitis
F. Henry Ellis, Jr., Mayo Clinic, Rochester, Minnesota

Esophageal Reconstruction with Colon Transplant
Paul F. Fox and David S. Jones, Stritch School of Medicine, Loyola University, Chicago, Illinois

The Mitral Valve—Dynamic Pathology and Surgery
Robert P. Glover, Julio C. Davila and Robert G. Trout, The Presbyterian Hospital, Philadelphia, Pennsylvania

Esophageal Replacement by a Reversed Gastric Tube
Henry J. Heimlich, New Rochelle, New York

Cardiac By-Pass and Elective Arrest with Autogenous Oxygenation
James A. Helmsworth, William R. Cole, James Neely and Ralph Shabetai, University of Cincinnati College of Medicine, Cincinnati, Ohio

Anomalies of the Aortic Arch — Development of the Aortic Arch
George H. Humphreys II, Columbia-Presbyterian Medical Center, New York, N. Y.

Left Heart Catheterization
G. H. Lawrence, Mason Clinic, Seattle, Washington

The Anatomical Correction of the Tetralogy of Fallot Defects Under Direct Vision, Utilizing the Pump-Oxygenator
C. Walter Lillehei, Richard A. DeWall, Herbert E. Warden, and Richard L. Varco, University of Minnesota Medical School, Minneapolis, Minnesota

A Syndrome of Congenital Defects Involving the Abdominal Wall, Diaphragm, Sternum, Heart and Pericardium
Mark M. Ravitch, Baltimore City Hospitals, Baltimore, Maryland

Mitral Commissurotomy
John V. Thompson and E. R. Eaton, Methodist Hospital, Indianapolis, Indiana

Excision of Epiphrenic Diverticulum of the Esophagus
Hawley H. Seiler, St. Joseph's Hospital, Tampa, Florida

ANNUAL CONVENTION, STUDENT AMERICAN MEDICAL ASSOCIATION

The 7th Annual Convention of the Student American Medical Association will be held at the Morrison Hotel, Chicago, May 1-4. More than a score of prominent physicians have accepted invitations to participate in the first full-scale scientific sessions, to be presented with the cooperation of the American College of Chest Physicians, the American College of Obstetricians and Gynecologists, and the William S. Merrell Company.

Dr. Theodore H. Noehren, Buffalo, New York, representing the Council on Undergraduate Medical Education of the American College of Chest Physicians, has arranged the following program to be presented Friday morning, May 2:

Presiding: Burgess L. Gordon, Albuquerque, New Mexico, President, American College of Chest Physicians
"The Incidence of Pulmonary Tumors in Mice Exposed to Aerosols of Therapeutic Agents"
James T. Post, Portland, Oregon (winner, 1957 College Essay Contest)
Discussion: David B. Radner, Chicago, Illinois
"Heart Surgery Today—Its Accomplishments and Promises"
Charles P. Bailey, Philadelphia, Pennsylvania
"Everything in the Book" (Discussion of 100 Cases of Chest Pathology) Theodore H. Noehren, Buffalo, New York
Discussion: Karl H. Pfuetze, Chicago, Illinois
X-ray Conference
Moderator: Herman J. Moersch, Rochester, Minnesota
Panel: J. Maxwell Chamberlain, New York City; John R. McDonald, Rochester, Minnesota; Colonel James A. Wier, Denver, Colorado

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College Chapter News

OKLAHOMA CHAPTER

A Pembine-type conference will be presented at the annual meeting of the Oklahoma Chapter, to be held jointly with the state Trudeau Society at the Western Hills Lodge, Waggoner, April 19-20. The program is as follows:

Saturday, April 19—Moderator: Richard M. Burke, Tulsa, President.
2:00 p.m. Introductory remarks: J. Floyd Moorman, Oklahoma City, President, Oklahoma Trudeau Society
"Ten Consecutive Admissions with Pulmonary Histoplasmosis, Missouri State Sanatorium, Mount Vernon"
"Evaluation of Pulmonary Function Studies"
Medical interpretation—William W. Stead, Gainesville, Florida
Surgical interpretation—Harry E. Walkup, Oteen, N. C.
6:00 p.m. Social hour
7:00 p.m. Dinner—James F. Hammarsten, Oklahoma City, presiding
Guest speaker: Harry E. Walkup
Sunday, April 20—Moderator: Allen E. Greer, Oklahoma City
9:00 a.m. "Ten Cases with Silico-tuberculosis Seen Prior to December, 1957, Eastern Oklahoma Tuberculosis Sanatorium"
Forrest P. Baker, Talihina
"Ten Consecutive Pulmonary Resections with Postoperative Space Problems"
Harley C. Darnall, State Sanatorium, Arkansas
12:15 p.m. Luncheon
Afternoon session—J. Lewis Yates, Mt. Vernon, Missouri
1:30 p.m. "A Group of Discharges with Collagen Vascular Disorders, Western Oklahoma Tuberculosis Sanatorium"
Glen P. Dewberry, Clinton
Critique
William W. Stead, Harry E. Walkup
4:00 p.m. Business meeting

MISSOURI CHAPTER

A joint meeting of the Missouri Chapter of the College and the Missouri Trudeau Society will be held at the Hotel Statler, St. Louis, Sunday, April 13. The program is as follows:

11:30 a.m. Business meetings
12:00 noon Luncheon
1:00 p.m. "Benign Obstructing Lesions of the Esophagus"
Duane Carr, Memphis, Tennessee
"Cineangiocardiography Method and Demonstration"
J. Girard Mudd, St. Louis
"Progress Report on Combined Therapy of Tuberculosis Using Pyrazinamide"
Bernard Friedman and Mario Pianetto, St. Louis

NEW JERSEY CHAPTER

The New Jersey Chapter will meet in Atlantic City, May 21, in conjunction with the annual meeting of the state medical society. The following program will be presented:

10:00 a.m. "Endoscopic Therapy of Lung Abscess"
A. Albert Carabelli, Trenton
"Fluoroscopic Determination of Pulmonary Stenosis—A New Sign"
Henry Green, Newark
"Familial Pulmonic Stenosis and Deaf Mutism—Clinical and Genetic Considerations"
Sanford M. Lewis, Lawrence Gilbert, David Biber, and Benjamin B. Sonnenblick, Ph.D., Newark
"Evaluation of Pleural Biopsy"
William B. Abrams, Maurice J. Small, East Orange
"Use of Meticorten in Chronic Pulmonary Tuberculosis"
Paul K. Bornstein, Asbury Park; Israel G. Epstein, G. Nair, Brooklyn, New York
12:30 Luncheon and business meeting

NEW ENGLAND STATES CHAPTER

The next monthly meeting of the New England States Chapter will be held at St. Vincent's Hospital, Worcester, Massachusetts, April 19. The following program will be presented:

9:00 a.m. Chairman: Heinz J. Lorge, Worcester, Massachusetts
Joint session with surgical section of St. Vincent's Hospital. Presentation of thoracic problems by Drs. Paul Ware, Oscar Ware and Oscar Feinsilver, Worcester:
"Pulmonary Sarcoidosis Associated with Bullous, Obstructive Emphysema" and "Cardiac Decompensation due to Co-existing Mitral Stenosis with Obliterative Pleuritis"

Symposium on Tuberculosis:
"The Present Status of Chemotherapy"
Paul Dufault, Rutland, Massachusetts
"The Changing Aspects of the Pathology of Pulmonary Tuberculosis"
Oscar Auerbach, East Orange, New Jersey
"Evaluation of the Available Techniques for Estimating the Virulence of the Tubercle Bacillus"
William Steenken, Jr., Saranac Lake, New York
"Ambulatory Treatment of Pulmonary Tuberculosis"
Emil Rothstein, Brockton, Massachusetts
"Pulmonary Embolism, Roentgenological Manifestations"
Felix G. Fleischner, Boston
12:50 p.m. Luncheon

2:00 p.m. Chairman: Rudolph Kurzmann, Cambridge, Massachusetts
"Principles of the Ventilatory Response in Pulmonary Emphysema"
Alvan L. Barach, New York City
Discussion: Maurice S. Segal, Boston
"Circulatory Diseases of the Lungs"
Robert P. McCombs, Boston
"Management of Diagnostic Problems Associated with Cancer of Lung"
Max G. Carter, New Haven, Connecticut
"The Present Status of Management of Carcinoma of the Esophagus"
John W. Strieder, Boston
"Results of Megavoltage Therapy of Esophageal Carcinoma and Cancer of the Lung"
Wayne P. Whitcomb, New Haven, Connecticut
Discussion: Richard H. Overholt, Boston

6:00 p.m. Dinner—Stockholm Restaurant. Welcome by Maurice S. Segal, Boston, chapter President.
Guest speaker: Dr. Hudson Hoagland, Executive Director, Worcester Foundation for Experimental Biology—"Basic Research in the Field of Cancer at the Worcester Foundation for Experimental Biology"

A tour of the city, including the Worcester Art Museum and Old Sturbridge Village, is being planned for the ladies. For advance dinner reservations ($6.00 each), please contact Dr. Oscar Feinsilver, 390 Main Street, Worcester 8, Massachusetts.

OHIO CHAPTER

The annual meeting of the Ohio Chapter will be held at the Netherland-Hilton Hotel, Cincinnati, April 16, in conjunction with the state medical association meeting. After luncheon at 12:00 noon, the following program will be presented:

"Experience in the Management of Spontaneous Pneumothorax"
Harvey Mendelsohn, Cleveland
"The Tuberculous Patient Two Years after Discharge from the Hospital"
Harold Humphrey, Columbus
"Surgical Treatment of Stenotic and Insufficient Lesions of the Aortic Valve"
Elmer Maurer, Cincinnati
"Trends in Tuberculosis as Demonstrated by Recent Hospital Admissions"
Herman Nimitz, Cincinnati

WISCONSIN CHAPTER

The Wisconsin Chapter will hold its annual meeting at the Schroeder Hotel, Milwaukee, Monday, May 5. The following program will be presented:

2:00 p.m. "Disseminated Indeterminate Pulmonary Lesions"
John R. McDonald, Rochester, Minnesota
"Significance of Heart Sounds in Clinical Medicine"
Aldo A. Luisada, Chicago, Illinois
"Physiologic Effects of Exercise in Pulmonary Emphysema"
Edwin R. Levine, Chicago, Illinois
"An Analysis of the Radiation Hazards and Rewards of Chest X-rays"
Jerome L. Marks, Milwaukee
"Physiologic Defects in Pulmonary Diseases"
George R. Meneely, Nashville, Tennessee
Panel discussion of subjects presented, with questions from the floor.

ARIZONA CHAPTER

The annual meeting of the Arizona Chapter will be held in Chandler, Thursday, May 1. Following a luncheon at 12:15, Dr. D. W. Melick, Phoenix, President, will preside over the business meeting. Dr. William B. Steen, Tucson, President-Elect, will preside over the following scientific program:

"Steroids in the Treatment of Patients Suffering from Pulmonary Tuberculosis"
Leo V. DiCara, Tucson
"Fungizone and Coccidioidomycosis"
Hans F. Stein, Tucson
"Report of VA-Armed Forces 17th Conference on Chemotherapy of Tuberculosis"
Solomon Netzer, Tucson
"Graphic Diagnosis of Pulmonary Heart Disease"
Hyman Fisher, Tucson
"The Middle Lobe Syndrome"
Leon L. Titche, Tucson

FLORIDA CHAPTER

The annual meeting of the Florida Chapter will be held at the Americana Hotel, Miami Beach, Sunday, May 11. The following program will be presented:

8:45 a.m. Business meeting
9:10 a.m. "Association of Chronic Obstructive Pulmonary Emphysema with Chronic Peptic Ulceration"
Louis Zasly, Delray Beach
"A Comparison of Clinical with X-ray and Pulmonary Function Laboratory Estimation, Timed and Total Vital Capacity"
Milton B. Cole, Bay Pines
"Dysphagia"
Myron I. Segal, Hollywood
"Clinical Significance of Solitary Pulmonary Nodules: 60 Collected Cases with Roentgenologic and Pathologic Correlations"
Franklin G. Norris, Orlando
"Anticoagulants in Impending Myocardial Infarction"
E. Sterling Nichol, Miami
"The Use of Prednisolone in Far Advanced Pulmonary Tuberculosis: Report of Four Seriously Ill Colored Females Who Had Failed to Respond to Conventional Therapy"
Mary Lou McIlhany, Lantana
"Management of Carcinoma of the Lung in Elderly and Poor Risk Patients"
DeWitt C. Daughtry, Miami
12:00 noon Luncheon
1:00 p.m. "Fungus Diseases of the Lungs"
David T. Smith, Durham, North Carolina
"Surgical Aspects of Diaphragmatic Hernia"
James Moody, Orlando
X-ray Conference (physicians are requested to bring x-rays for discussion after presenting a brief clinical history)

NEWS NOTES

Dr. Arthur M. Olsen, Rochester, Minnesota, visiting physician pro tem of the Lovelace Foundation, Albuquerque, New Mexico, spoke on "Pulmonary Complications of Esophageal Disease" and "Esophageal Motility Studies" during a two-day scientific session in Albuquerque March 6 and 7. In addition, Dr. Olsen participated in several panel discussions dealing with pulmonary and esophageal disease.

Dr. J. L. Ehrenhaft, Iowa City, Iowa, recently spoke at a scientific seminar sponsored by the Northwest Iowa Heart Council, the Clay County and Northwest Iowa Medical Societies in Spencer.

DISEASES of the CHEST

VOLUME XXXIII MAY, 1958 NUMBER 5

A Rapid Method for Analysis of Spirographic Tracings in Pulmonary Function Testing

ROSS C. KORY, M.D., F.C.C.P
Milwaukee, Wisconsin

In recent years, pulmonary function testing has emerged from a primarily research activity carried on in only a few scattered laboratories, to a clinical function of steadily increasing importance in the diagnosis and management of pulmonary disease. This evolution has been in part due to the simplification of techniques and equipment. With increasing clinical employment of these techniques, it is important to simplify and accelerate these measurements. One of the time consuming aspects of such testing is the analysis of spirographic tracings. The methods described in this report are designed to provide more rapid analysis and measurements of spirograms without loss of accuracy.

The most widely used instruments for ventilatory measurements are the nine and 13-½ liter Collins Respirometers, which provide an ink recorded spirographic tracing together with a cumulative record of ventilation by means of a second pen attached to a Reichert ventilograph.[1] Tracings obtained with these instruments can provide the following measurements: resting minute ventilation and oxygen consumption, total vital capacity, timed expiratory volumes, inspiratory and expiratory flow rates, maximum breathing capacity, functional residual capacity by helium dilution, and bronchospirometry. Although the techniques as described are for use with Collins spirometers, they may easily be adapted for use with other instruments.

These techniques are based on a new "slide rule" which by a simple refinement of the Segal-Herschfus ruler[2] provides more rapid and convenient measurements of spirographic tracings.

Method

The method consists of: (a) A multi-purpose "slide rule" for measurement of the various tracings, and (b) appropriate tables which con-

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From the Cardiopulmonary Laboratory and Research Service, Wood Veterans Administration Hospital and the Department of Medicine, Marquette University School of Medicine.

*These slide rules may be obtained from Presco Plastics, Inc., Milwaukee, Wisconsin.

**The spirometer bells for the Collins nine and 13½ liter respirometer are now standardized at 20.73 cc./mm. and 41.27 cc./mm. respectively.

The author is indebted to Jacqueline Owenby, B.S. and Helen Delfeld, B.S for their useful suggestions in connection with these methods.

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vert the slide rule measurements to gas volumes corrected for temperature and barometric pressure.

The "slide rule" as illustrated in Figure 1 consists of a transparent plastic ruler* with four large vertical divisions each 32 mm. wide. This width corresponds to 12 seconds for the rapid kymograph speed of the Collins Respirometer and one minute for the slow kymograph speed of that instrument. The center two divisions have vertical rulings identical with the Segal-Herschfus ruler with 12 equal sub-divisions each representing one second at the rapid kymograph speed. The outer two divisions are ruled horizontally in millimeters, the left scale reading 0 to 150 mm. upward, and the right scale 0 to 150 mm. downward. The horizontal lines across the entire rule at each 50 mm. point are used to orient the ruler properly on the spirographic paper. Finally a slide with a hairline is provided which slips up and down the length of the ruler.

A second longer slide rule (Fig. 2) is available which differs only in that the millimeter scale reads from 0 to 300. This rule is designed primarily for use for measuring vital capacity tracings on the nine liter respirometer or similar spirometers with a small bell.

Two tables are utilized for a given spirometer. The tables shown are for the 13-½ liter Collins spirometer but may just as easily be constructed for the Collins nine liter instrument or any other spirometer. Table I is used for vital capacity and oxygen consumption determinations and includes simply the bell factor (41.27 cc/mm for the 13 ½ liter instrument)* together with the temperature corrections as outlined by Comroe[3]

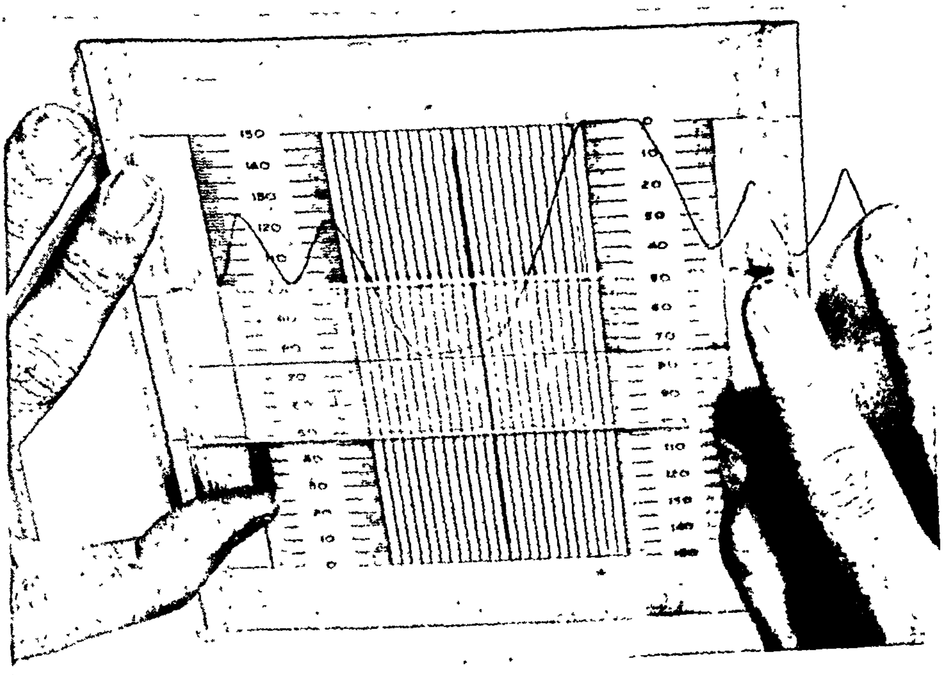

FIGURE 1: The 0-150 mm. pulmonary function slide rule superimposed upon a spirographic tracing. The tracing itself stands out distinctly because of the unlined paper used with this method.

to convert the gas volume to body temperature and pressure, saturated (BTPS). Table II is used in those measurements utilizing the ventilograph pen (resting minute ventilation and maximum breathing capacity) and incorporates: (a) the bell factor, (b) the ventilograph gear factor[1] of the particular, instrument, (c) the factor "5" for converting the actual 12 second test to 60 seconds, thereby expressing the maximum breathing capacity in liters per minute, and (d) the temperature correction factor.[3]

Use of Method in Various Spirometric Determinations

The techniques described below apply to tests performed with either the nine liter or 13-½ liter Collins respirometer. The actual performance of these tests have been adequately described elsewhere.[3]

For use of these methods with instruments other than Collins respirometers, it is necessary only to determine the *actual* time interval represented by 32 mm. on the kymograph tracings and the actual volume of air per millimeter of pen excursion (bell factor) for the particular spirometer. Appropriate tables may then be constructed for the particular instrument.

TABLE I

CONVERSION OF VITAL CAPACITY AND OXYGEN CONSUMPTION TRACINGS TO BTPS* CORRECTED GAS VOLUMES (milliliters)
for Collins 13½ liter Respirometer

Bell factor: 1 mm. of pen deflection = 41.27 ml.

Formula for calculation of table:

Volume of gas corrected to BTPS* = mm. of pen deflection × 41.27 (Bell factor) × BTPS* correction factor

Pen Deflection in Mm.	ATPS**	Temperature of spirometer gas in °C										
		22	23	24	25	26	27	28	29	30	31	32
1	41	45	45	45	44	44	44	44	43	43	43	43
2	83	90	90	89	89	88	88	87	87	86	86	85
3	124	135	134	134	133	132	132	131	130	129	129	128
					*	*	*					
148	6108	6670	6630	6602	6573	6530	6499	6456	6425	6383	6346	6309
149	6149	6715	6678	6647	6617	6574	6543	6499	6468	6426	6389	6352
150	6190	6751	6723	6692	6661	6618	6587	6543	6512	6470	6432	6394

*BTPS —Body temperature, pressure, saturated with water: correction factor according to Comroe.[3]

**ATPS—Ambient temperature, pressure, saturated with water (no temperature correction).

*** —In order to save space, only the first three and last three lines of the table are shown here. The complete table will be available with reprints of this paper.

1. Total Vital Capacity Volume and Time

The vital capacity tracing is usually obtained with the rapid kymograph speed (32 mm. in 12 seconds). The slide rule is superimposed upon the tracing as shown in the upper right portion of Figure 3. The rule is placed so that the intersect just to the left of the upper zero mark (Fig. 3-A) is superimposed upon the tracing at the point of maximal inspiration just as the expiratory curve begins, and the ruler is correctly oriented. The slide hairline is then slipped down to the point of maximal expiration (Fig. 3-B) and the number of millimeters is read on the right hand mm. scale. With this millimeter reading and the temperature, the total vital capacity in millimeters corrected to BTPS may be rapidly obtained from Table I. While the ruler is still in place, the duration of the vital capacity expiration is read directly in seconds on the vertical lined scale reading from line "A" to point "B." In Figure 3 this is exactly four seconds.

2. One, Two and Three Second Expiratory Volumes

The purpose of these measurements is the determination of the rapidity with which air can be expired. Thus the volume of air which can be ex-

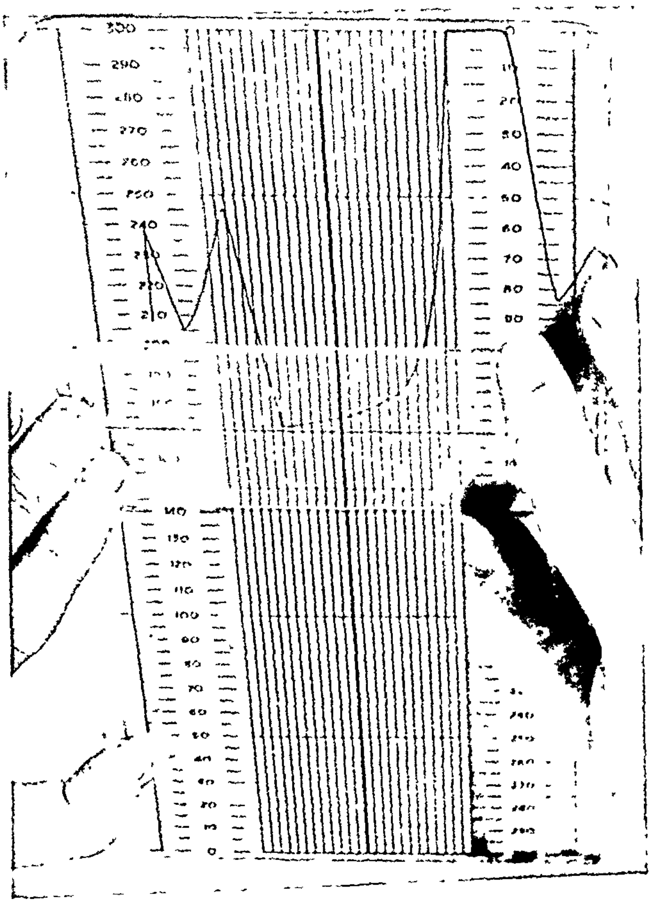

FIGURE 2: The longer (0-300 mm.) slide rule used particularly with tracing made on the 9 liter spirometer.

pired in one, two and three seconds is measured and may be expressed both in actual volume and in per cent of the total vital capacity.[4]

For these measurements, the slide rule is placed so that intersect "A" (Fig. 3) is superimposed upon the point of maximal inspiration at the beginning of the expiratory curve just as for the total vital capacity. The hairline is then slipped down to the intersect between the one second vertical division and the expiratory tracing itself (Fig. 3-1) and a reading in millimeters is made on the right hand mm. scale. The hairline is then slipped down to the two second intersect (Fig.3-2) and another similar reading taken. This is repeated for the three second intersect (Fig. 3-3). Each of these millimeter readings for the one, two and three second expiratory volume together with the temperature will provide the volume in millimeters corrected to BTPS by referring to Table I. The per cent of the total VC would be

$$\frac{\text{1 sec. expiratory volume x 100}}{\text{Total vital capacity}}$$

with a similar ratio for the two second and three second expiratory volumes.

TABLE II

MAXIMUM BREATHING CAPACITY TABLE: for Collins 13½ liter Respirometer

Bell factor—41.27 cc./min. Ventilograph gear factor—11.09

The mm. in the left column refers to the mm. deflection of the ventilograph pen in a 12 second breathing period. The MBC value for this mm. deflection is read directly in liters per minute under the appropriate temperature column.

Formula for calculating table:

MBC in liters per min. corrected to BTPS* = mm. of Ventilograph pen deflection in 12 sec. × Bell factor (41.27) × Ventilograph gear factor (11.09) × 5 (to convert liters in 12 sec. to liters per minute) × BTPS* correction factor

Ventilograph Pen deflection 12 sec. in Mm.	ATPS**	Temperature of spirometer gas in °C. 22	23	24	25	26	27	28	29	30	31	32
1	2	2	2	2	2	2	2	2	2	2	2	2
2	5	5	5	5	5	5	5	5	5	5	5	5
3	7	7	7	7	7	7	7	7	7	7	7	7
					* * *							
98	224	245	244	242	241	240	239	237	236	234	233	231
99	227	247	246	245	244	242	241	240	239	237	236	234
100	229	250	248	247	246	245	244	242	241	239	238	237

*BTPS —Body temperature, pressure, saturated with water: correction factor according to Comroe.[5]

**ATPS—Ambient temperature, pressure, saturated with water (no temperature correction).

*** —In order to save space, only the first three and last three lines of the table are shown here. The complete table will be available with reprints of this paper.

3. *Oxygen Consumption*

This test is performed with the slow kymograph speed (32 mm. = one minute), the tracing recording several minutes of breathing. The usual oxygen consumption baseline is drawn in the conventional manner connecting the expiratory points. The slide rule is then placed on the spirogram such that the intersect C (Fig. 3) on the slide rule is oriented on the paper and the hairline brought to the intersection of the O_2 baseline with the extreme vertical line (D) on the ruler. The reading is made on the left hand scale in millimeters and is corrected to a dry gas volume at 0° C and 760 mm. Hg (STPD) by means of a correction factor obtained from a readily available nomogram.[5]

4. *Maximum Breathing Capacity*

The maximum breathing capacity (MBC) is performed as described by Motley et al[6] employing a 12 second period of maximum voluntary hyperventilation with the kymograph drum moving 32 mm. in 12 seconds. For the MBC, the ventilograph tracing is used and a line is drawn defining the slope. Figure 4 shows the slide rule in place for this measurement. The lower left intersect just to the right of the zero mark (Fig. 4-E) is superimposed upon the beginning of the MBC ventilograph tracing. The hairline is then brought to the intersection of the ventilograph tracing and the extreme left vertical line on the rule (Fig.

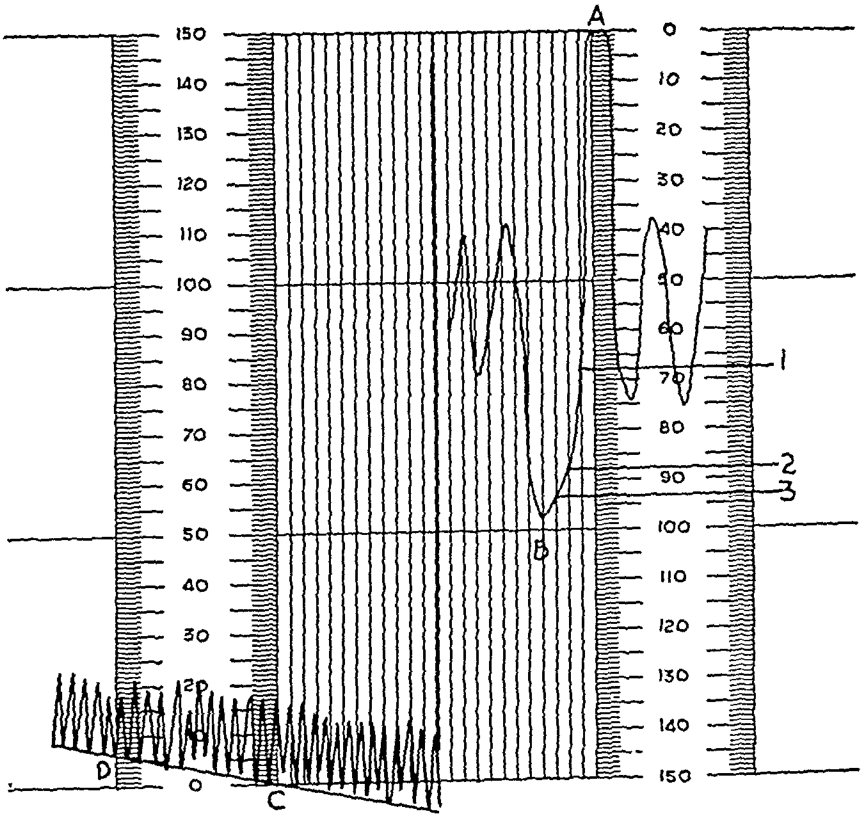

FIGURE 3: Diagram of the rule as used for vital capacity and oxygen consumption

4-F) and the number of millimeters read from the left hand scale. With this mm. reading and the temperature, the BTPS-corrected maximum breathing capacity can be read directly from Table II in liters per minute.

5. *Resting Minute Ventilation*

In this test the kymograph is run at the slow speed (32 mm. = 1 min.) for several minutes. The slope of the ventilograph tracing is inscribed, and the measurement made exactly as for the maximum breathing capacity. However, since the resting minute ventilation is measured on the slow speed, (1/5 of the rapid speed), the liters per minute as recorded in Table II must be divided by five. Calculation may be further simplified by measuring a two-minute period (Fig. 4, G-H) and dividing the value obtained from Table 2 by 10.

6. *Maximal Midexpiratory Flow (Leuallen and Fowler*[7]*)*

The expiratory curve which appears steepest on gross inspection is selected. The zero mark of the right hand scale of the "slide rule" is placed at the peak of inspiration and the total vital capacity measured on the millimeter scale. This figure is divided by four to obtain the number of millimeters for ¼ of the vital capacity volume (VC/4). With the zero mark of the right scale still superimposed upon the peak of

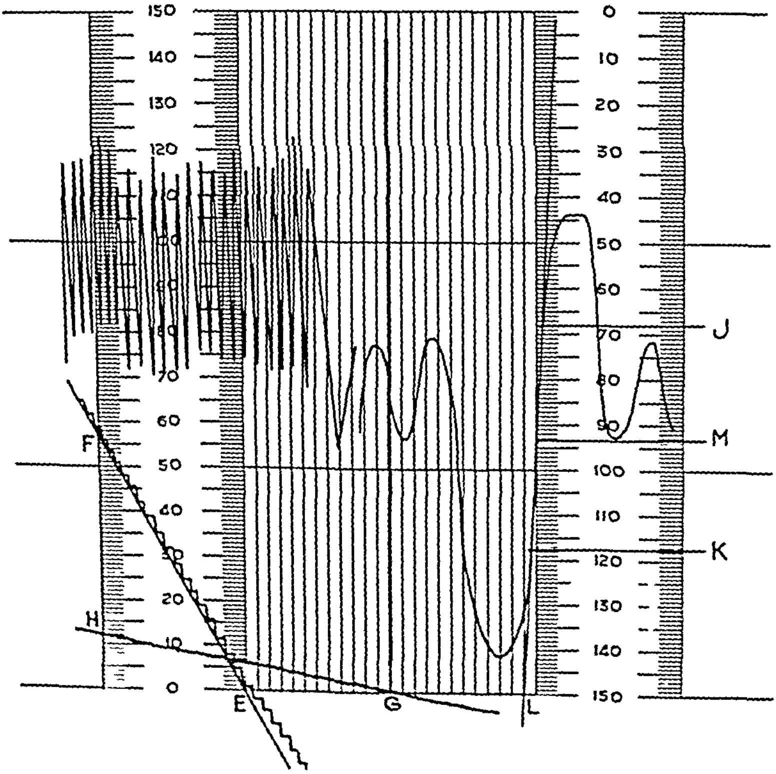

FIGURE 4: Diagram of the ruler as used for resting minute ventilation, maximum breathing capacity, and maximal mid-expiratory flow measurements.

inspiration, the number of millimeters of VC/4 is measured down the expiratory curve and a horizontal mark made with a thin pencil.

The zero mark of the *left* hand scale on the rule is then placed at the lowest point of expiration and the number of millimeters for VC/4 measured *up* the expiratory curve and a second horizontal mark inscribed. These steps have provided a point ¼ of the way *down* from peak inspiration (J) and a second point ¼ of the way *up* from maximal expiration (K).

A line is drawn connecting J and K (Fig. 4). The slope of this line expressed in liters per second is the maximal midexpiratory flow rate (MMEF).[7] This "MMEF slope" may be measured as follows: The point, one second to the left of the 150 mm. line on the right hand scale (Fig. 4-L) is superimposed upon the "MMEF" slope line, and the ruler oriented with vertical lines. The point at which this slope crosses the "zero second" line (Fig. 4-M) is read in mm. on the left hand scale. The number of mm. together with the temperature provides from Table I a BTPS-corrected volume which is the MMEF expressed in liters per second.

If the slope is extremely steep, it might be necessary occasionally to use the 300 mm. slide rule (Fig. 2). On the other hand if the slope is comparatively flat, it is better to superimpose the ruler on the slope at the two second point and divide the millimeter reading by two.

Discussion

At the present time, pulmonary function tests are being carried out in hundreds of hospitals and increasingly in doctor's offices. One of the limiting factors in practical pulmonary function testing is still the time-consuming nature of both the testing techniques and the analysis of the spirograms. The methods herein described will not only expedite the analysis of the tracings, but will provide somewhat greater accuracy even in the hands of an average technician. An additional benefit of this "slide rule" technique is that by inscribing periodic vertical lines on the kymograph paper with the writing pen (for proper positioning of the slide rule), plain unruled paper may be substituted for the more expensive ruled kymograph paper. With the unruled paper, the tracings stand out more clearly and may be measured more easily in the absence of the confusing horizontal lines.

SUMMARY

1. A method is described for more rapid and efficient analysis of spirographic tracings utilizing a new transparent plastic slide rule and tables prepared for direct conversion of millimeter measurements of spirographic tracings into actual volumes and flow rates.

2. This method provides simpler and slightly more accurate measurements of spirographic tracings, eliminates much calculation, and allows the use of unlined and much less expensive spirographic paper in carrying out these tests.

Addendum

Recently, many pulmonary function laboratories have begun to use more rapid kymograph speeds, especially for more accurate evaluation of expiratory flow curves. A new Collins spirometer (Stead-Wells) provides a rapid kymograph speed of 32 mm. per second. The kymographs of the older Collins instruments may be converted to this rapid speed by simply substituting a more rapid motor for either of the two kymograph motors now in use.

The "slide-rule" is easily adaptable to these rapid speeds, since one large vertical division (32 mm.) would represent one second instead of twelve seconds. At this rapid speed, 0.5 second equals six small vertical divisions which permit an accurate measurement of the 0.5 second expiratory capacity.

RESUMEN

1. Se describe un método para realizar un análisis más rápido y eficiente de los trazos espirográficos usando una nueva regla plástica transparente, de deslizamiento, preparada para la conversión directa de las medidas en milímetros de los trazos espirográficos en los volúmenes verdaderos y medidas de las corrientes gaseosas.

2. Este método provee de medidas más sencillas y algo más exactas para los trazos espirográficos, elimina muchos cálculos y permite el uso de papel sin rayar y mucho menos caro para la espirografía al hacer estas lecturas.

ZUSAMMENFASSUNG

1. Es wird eine Methode beschrieben, die eine schnellere und leistungsfähige Analyse von spirographischen Aufzeichnungen unter Verwendung einer neuen transparenten Plastik-Gleitrolle und von Tabellen, die zur direkten Umwandlung der Millimetermessungen der spirographischen Aufzeichnungen in tatsächliche Volumina und Durchströmungswerte bestimmt sind.

2. Diese Methode gewährt einfachere und ein wenig genauere Messungen spirographischer Aufzeichnungen, macht viele Berechnungen unnötigt und ermöglicht den Gebrauch von nicht-liniiertem und viel billigerem Spirographenpapier zur Vornahme dieser Teste.

REFERENCES

1 Reichert, P. and Roth, H.: "The Ventilograph: An Improved Recording Ventilometer and Its Applications," *J. Lab. and Clin. Med.*, 25:1091, 1940.

2 Segal, M. S., Herschfus, J. A. and Dulfano, M. J.: "A Simple Method for the Determination of Vital Capacity—Time Relationships," *Dis. Chest*, 22:123, 1952.

3 Comroe, J. H., Jr. and Kraffer, N. H.: "II. Measurement of Gas Volumes" in "Methods in Medical Research," Vol. 2, pp. 94-101, Year Book Publishers, Chicago, 1950.

4 Gaensler, E. A.: "Analysis of the Ventilatory Defect by Timed Vital Capacity Measurements," Trans. 47th Annual Meeting of Nat. Tuberc. Assn. 1, 1951.

5 Consolazio, C. F., Johnson, R. E. and Marek, E.: "Metabolic Methods," the C. V. Mosby Company, St. Louis, 1951, p. 334.

6 Motley, H. L.: "Clinical Pulmonary Physiology II. Detection of Early Lung Function Changes in Industrial Exposure," *Indust. Med. and Surg.*, 22:262, 1953.

7 Leuallen, E. C. and Fowler, W. S.: "Maximal Midexpiratory Flow," *Am. Rev. Tuberc. and Pulm. Dis.*, 72:783, 1955.

Steroid Acid Amides of Diamino Diphenyl Sulfone

ARPAD BERCZELLER, M.D.*
Staten Island, New York

For the past several years, I synthesized various new steroid compounds and steroid derivatives for chemotherapeutic purposes. The series of the steroid acid amides of diamino diphenyl sulfone included 4-cholylamino-4′-amino diphenyl sulfone (B110) and 4-desoxycholylamino 4′-amino diphenyl sulfone (B111) which were chosen among representative members of this group for more detailed study. A brief survey of experimental findings on B111 is presented.

Figure 1 shows the chemical composition of the compound. It is a mono-desoxycholic acid amide of diamino diphenyl sulfone. The colorless crystals are soluble in alcohol, acetone, propylene glycol. B111 is slightly soluble in distilled water, however, in serum, stable solutions of 200 mcg/ml concentration can be obtained.

The crystalline pure compound was tolerated by guinea pigs and mice without apparent toxicity in large single doses and prolonged continuous administration as in a drug diet. Thus, mice were given single doses orally corresponding to 12 grams (12000 mg.) per kilogram. Mice and guinea pigs were fed 1 per cent drug diet for two months. Mice were injected intravenously with doses corresponding to 180 mg. per kilogram. No toxic symptoms were observed after administration of these massive amounts and only the physical circumstances of the method of administration precluded a further increase of the test doses. B111 was well retained in the animal body. Figure 2 demonstrates drug levels in tissues and blood three hours after intravenous injection of 100 mg. B111. The drug was present in the tissues in appreciable concentration when only traces were detectable in the blood. The situation was similar in the guinea pig during oral administration of B111 in active anti-tuberculosis chemotherapy. These findings illustrate the limitation of the importance of blood levels as indicators of the resorption and retention of B111 in the body.

Table I shows the in vitro activity of B111 as tested on the H37Rv strain and on several freshly isolated, "wild," strains of human tubercle bacilli. B111 was added to the culture medium in 0.05 ml. volume of alchoholic drug solution. The minimal inhibitory concentrations ranged from 3.12 to 25 mcg/ml. It is significant that the activity of B111 was essentially similar to that of the highly toxic parent compound diamino diphenyl sulfone (DDS). The tests were done in Youman's medium plus 10 per cent horse serum. Essentially similar values were obtained in plain Youman's medium and Dubos' medium. However, Youman's medium plus horse serum is the preferred one since the serum content increases the stability of the drug solution in the medium. The sensitivity values of the tested

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*Director, Bacteriology Department, Sea View Hospital.

TABLE I

SENSITIVITY* OF H37Rv AND FRESHLY ISOLATED HUMAN STRAINS OF TUBERCLE BACILLI TO B 111, DDS, STREPTOMYCIN AND INH; YOUMAN'S MEDIUM PLUS 10% SERUM

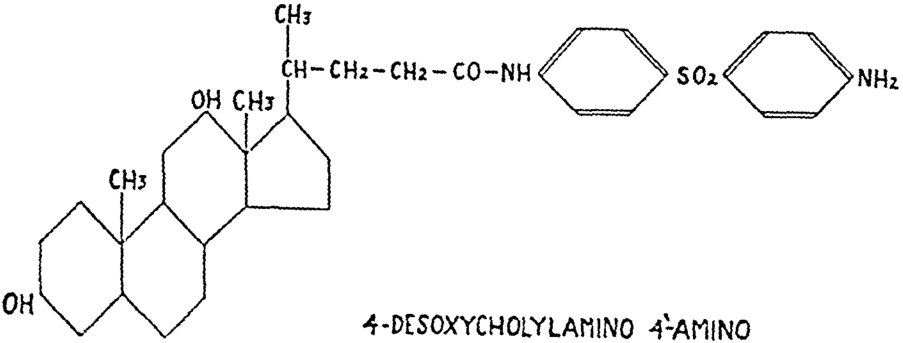
Strain	B 111	DDS	Streptomycin	INH
J. D.	6.25	6.25	10	10
S. K.	3.125	3.125	100	5
M. C.	25	25	<1	<0.1
C. M.	6.25	12.5	10	<0.1
M. B.	25	25	100	0.5
H. B.	12.5	12.5	10	<0.1
E. B.	3.12	3.12	10	>50
F. B.	12.5	12.5	1000	>50
R. C.	12.5	12.5	100	>50
G. G.	12.5	12.5	1000	10
W. H.	12.5	12.5	>1000	10
R. H.	3.12	6.25	>1000	10
H. Q.	12.5	12.5	10	10
F. S.	3.12	3.12	10	5
H37Rv	25	25	0.78	0.03

*Minimal inhibiting concentrations in mcg/ml.

strains to streptomycin and isoniazid indicate that there is no cross resistance between these agents and B111.

The mechanism of the action B111 was investigated by the method of infra red spectrography. The question as to whether the activity of B111 was due to the compound itself or to liberation of DDS was of crucial importance. Horse serum containing 100 mcg/ml B111 was incubated

FIGURE 1



4-DESOXYCHOLYLAMINO 4'-AMINO DIPHENYL SULFONE B111

TABLE II

THE EFFECT OF B 111 AND PROMIN ON GUINEA PIG TUBERCULOSIS RECORDED 90 DAYS AFTER SUBCUTANEOUS INOCULATION OF 0.1 mg. H37Rv. TREATMENT 1% DRUG DIET FOR 60 DAYS

	No. of Survivals No. of Animals	Degree of Tuberculosis*	Per cent of Maximal Involvement	Chemo-therapeutic Effectiveness**
Controls	7/12	12.1	75.6	0
B 111	12/12	2.2	13.7	5.5
Promin	10/12***	3.6	22.5	3.36

*maximum 16

**TB *of controls/treated*

***2 guinea pigs died 18 and 23 days after inoculation

at 37° C. for four weeks and then extracted with ethyl alcohol and acetone. The dried residue of the evaporated extract was analyzed by means of infra red spectral comparison. Figures 3, 4 and 5 show the infra red spectra of desoxycholic acid, DDS and B111 respectively. Figure 6 shows the infra red spectrum of the serum extract. The spectral comparison of this material with B111, DDS and desoxycholic acid clearly showed that the serum extract contained the intact B111. There was no evidence of either DDS or desoxycholic acid.

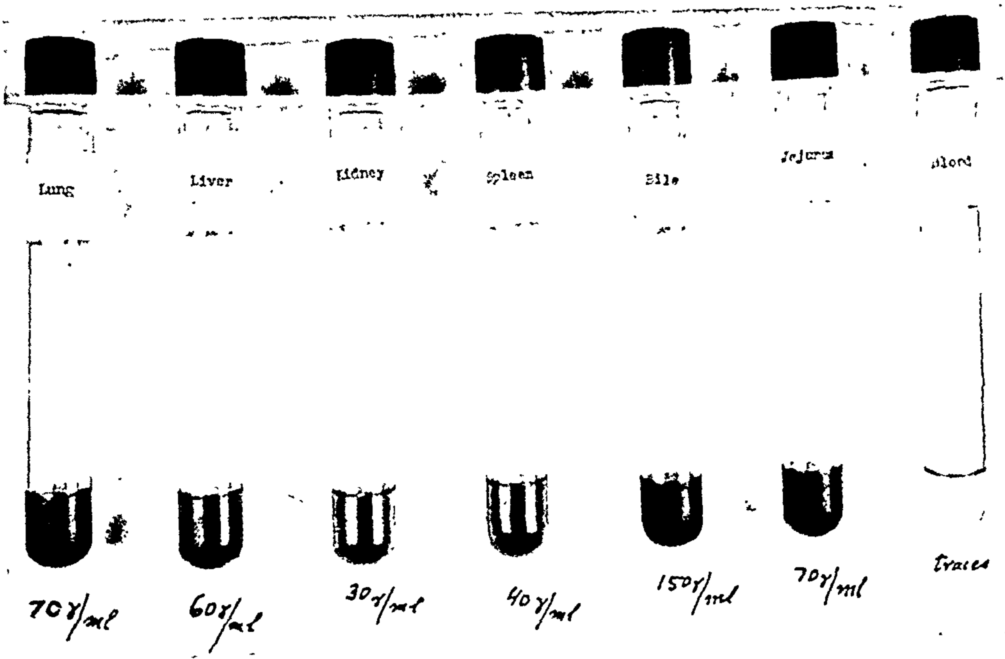


FIGURE 2: Drug levels in tissues and blood of rabbit three hours after intravenous injection of 100 mg. B 111. Marshall test in ethyl alcohol extracts of blood and tissues.

Table II demonstrates the effect of the oral administration of B111 on well established experimental guinea pig tuberculosis. The activity of B111 in suppressing the infection compared favorably with that of a standard toxic sulfone, promin. In experimental mouse tuberculosis, the suppressive effect of B111 was essentially similar to that found with other, but toxic, N-substituted sulfones.

In mixtures of B111 with streptomycin, synergism with striking bacteriostatic and bactericidal effects on tubercle bacilli was found.

Table III illustrates the combined bacteriostatic action of B111 and streptomycin. In the presence of one-half of the minimal inhibiting concentration of B111, there was a 16 fold potentiation of streptomycin. Bacteriostasis was obtained with a minute concentration such as 0.048 mcg/ml streptomycin. In the presence of 1/250 of the minimal inhibiting concentration of B111, equal to 0.1 mcg/ml there was a four fold increase of the original streptomycin potency. In previous studies on the combined action of streptomycin and dihydro-streptomycin with isoniazid on tubercle bacilli, the optimal effect was restricted to simple addition. The findings were similar with other combinations of the presently used anti-tuberculosis drugs.

Table IV and Figure 7 demonstrate the bactericidal effect of B111-streptomycin mixtures. The sterilizing effect within 48 hours as obtained with streptomycin alone at the prohibitive concentration of 10,000 mcg/ml was reproduced in mixtures with B111 at the "clinical" level of 10 mcg/ml streptomycin. The conditions of the test were exacting since the bacillary contents of full Dubos' cultures (0.1 mg. bacilli) were subcultured on Petragnani tubes. The plating method with serial dilutions is sensitive to comparatively small changes in the census of the surviving bacillary population. The method used in this experiment is only suitable for the demonstration of massive bactericidal action approaching complete sterilization.

The correlation of the pharmacological and antibacterial properties of these compounds was unexpected. It has been known that the reduction

TABLE III

SYNERGISM OF B 111 AND STREPTOMYCIN (S) BACTERIOSTATIC EFFECT

Combined Action of B 111 and Streptomycin on Human Tubercle Bacilli in Dubos' Medium

Minimal Inhibiting Concentrations mcg/ml		Bacteriostatic Units	
B 111	S	B 111	S
25	0	1	0
0	0.78	0	1
12.5	0.048	1/2	1/16
1	0.095	1/25	1/8
0.1	0.19	1/250	1/4
0.01	0.78	1/2500	1

of the toxicity of the sulfones as obtained by blockage of one or both amino groups of DDS has always been parallelled by a corresponding reduction of activity. Moreover, it was repeatedly demonstrated that any *in vitro* and *in vivo* activity of the derivatives was due to hydrolysis and

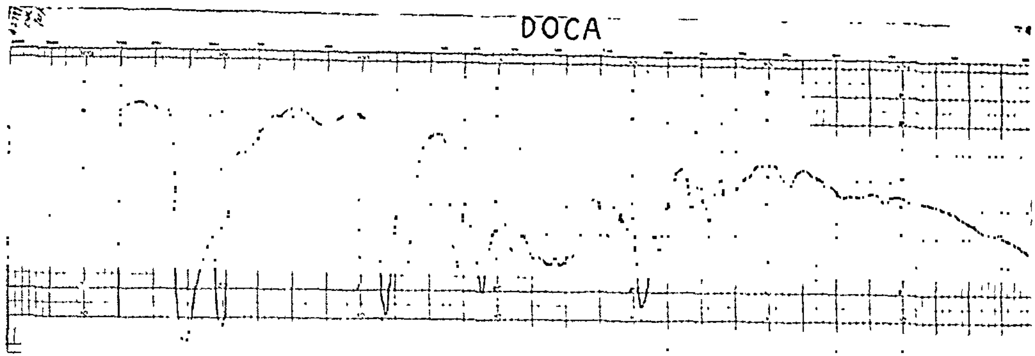


Fig. 3

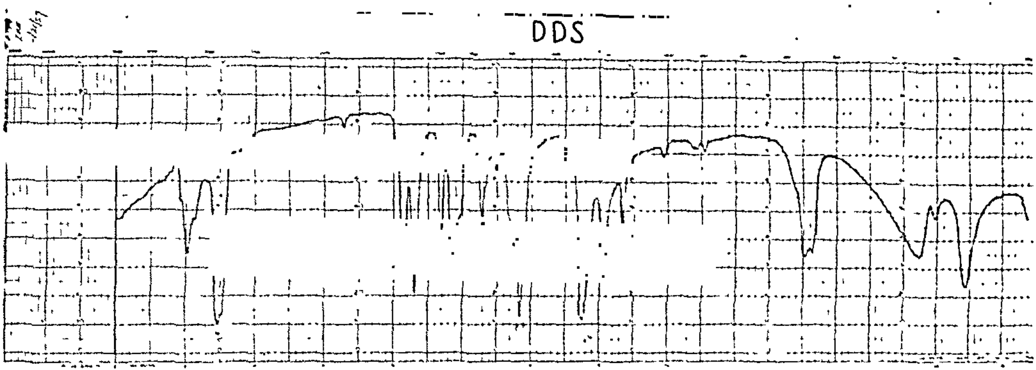


Fig. 4

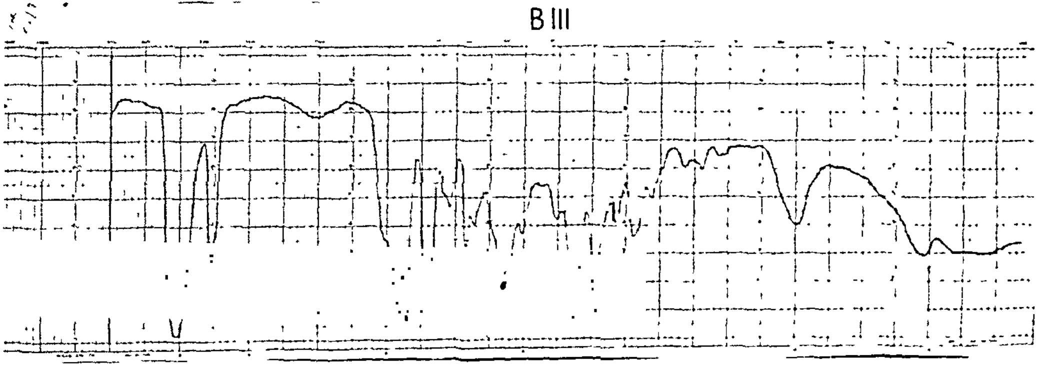


Fig. 5

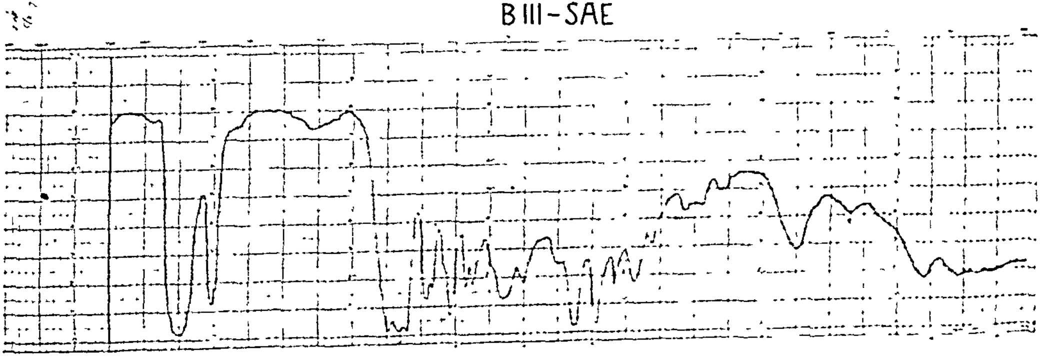


Fig. 6

Figure 3: Infra red spectrum of desoxycholic acid.—*Figure 4:* Infra red spectrum of 4,4′-diamino diphenyl sulfone.—*Figure 5:* Infra red spectrum of B 111.—*Figure 6:* Infra red spectrum of dried residue of alcohol-acetone extract of horse serum containing 100 mcg/ml B 111 incubated at 37°C for four weeks.

TABLE IV

SYNERGISM OF B 111 AND STREPTOMYCIN (S) BACTERICIDAL EFFECT

Subcultures of Washed Human Tubercle Bacilli on Petragnani's Medium after Exposure of Bacilliary Suspensions to Drugs in Dubos' Medium for 48 Hours

Drug Concentration* in Dubos' Medium		Petragnani Cultures	Drug Concentration* in Dubos' Medium		Petragnani Cultures
Streptomycin	B 111		Streptomycin	B 111	
1	0	4+	1	5	2+
10	0	4+	10	5	few colonies
100	0	3+	100	5	few colonies
1000	0	2+	1000	5	0
10000	0	few colonies	10000	5	0
0	0	4+			
0	5	3+			

*mcg/ml

liberation of DDS. Thus acylated derivatives are practically inactive *in vitro.* Their activity *in vivo* is dependent upon partial hydrolysis to DDS with corresponding reappearance of chronic toxicity. However, the activity of B111 is due to the compound itself as proved by infra red spec-

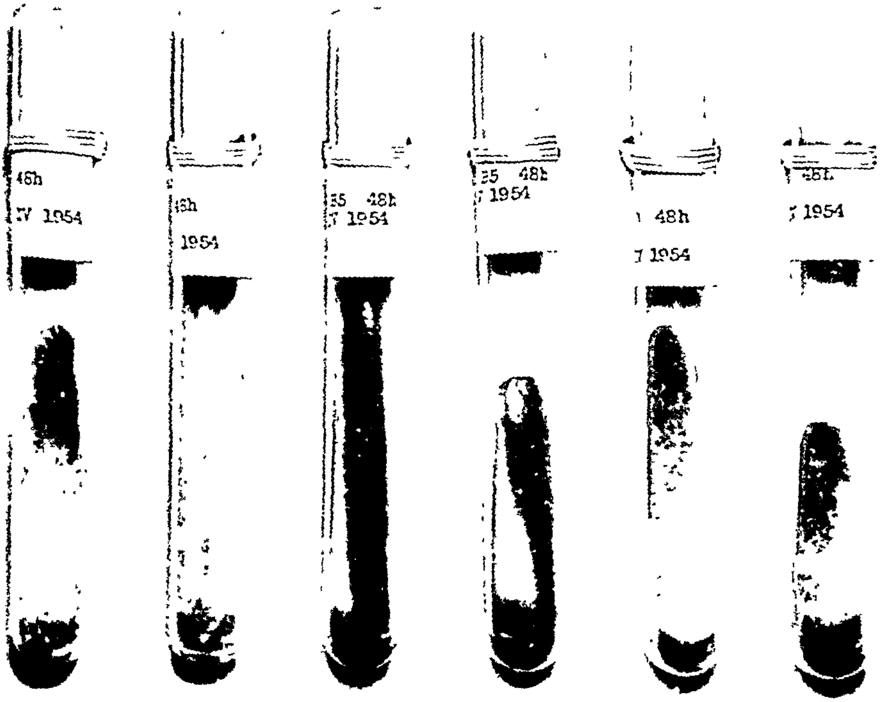


FIGURE 7: Bactericidal effect of B 111-Streptomycin mixtures. Subcultures of washed human tubercle bacilli on Petragnani's medium after exposure of bacillary suspensions to drugs in Dubos' medium for 48 hours. 1) Control; 2) 5 mcg ml B 111; 3) and 4) 100 mcg ml streptomycin plus 5 mcg ml B 111; 5 and 6) 100 mcg ml streptomycin.

trography. The high *in vitro* and *in vivo* activity without apparent toxicity of B110 and B111 are unique qualities for drugs of this type. The results indicate that the substituents used in these compounds are not inert blocking agents of all biological activities, but are detoxifiers on the one hand and chemotherapeutic activators on the other hand. The failures of previous sulfone therapy in the treatment of human tuberculosis were explained by the inadequacy of the tolerated dosage. In view of the data summarized above, B110 and B111 were recommended for a therapeutic trial in humans using full weight for weight doses which were active, but non-toxic in the animal experiments. In a preliminary clinical study with B111 done by E. H. Robitzek and I. J. Selikoff at Sea View Hospital,* the administration of such doses proved to be perfectly feasible.

The bactericidal synergism of these compounds and streptomycin appears to offer a new and potent anti-tubercular drug combination.

SUMMARY

A series of steroid acid amides of diamino diphenyl sulfone was synthesized and explored for chemotherapeutic activity.

4-desoxycholylamino 4′-amino diphenyl sulfone (B111), a representative member of this new group of compounds was tolerated in large amounts by experimental animals without toxic symptoms when administered orally or intravenously.

It was active *in vitro* on "wild" and laboratory strains of Myco. tuberculosis and active *in vivo* in experimental animal tuberculosis in the range of diamino diphenyl sulfone and other, but, toxic derivatives of DDS.

Activity of B111 was due to the unhydrolized compound as documented by infra red spectral comparisons. The steroid moiety of the compound appears to act simultaneously as a detoxifier and a chemotherapeutic activator.

In mixtures with streptomycin, synergism with striking bacteriostatic and bactericidal effects on Myco. tuberculosis was observed.

In a preliminary clinical study, the administration of large doses of B111 was perfectly tolerated by humans.

RESUMEN

Se investigó la actividad quimioterápica de una serie de substancias sintetizadas de los esteroides aminoácidos de la diamino difenil sulfona.

El 4-desoxicolilamino 4′-amino difenil sulfona (B 111), un compuesto representativo de este grupo se toleró en grandes cantidades por los animales de experiencia sin efectos tóxicos ya sea por vía oral o intravenosa.

Fué activo en cepas "silvestres" o de laboratorio del micobacterium tuberculosis y activo en los animales de experiencia tanto como las diaminodifenilsultonas u otras que son derivados tóxicos de la DDS.

La actividad del B 111 se debe a un compuesto no hidrolizado según lo que informa la comparación espectral infra-roja. La mitad esteroide del

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*This study was made possible by grants in aid of the Lasker Foundation and the New York Foundation used to cover expenses for the production of B 111.

compuesto parece actuar como desintoxicante y como activador quimioterápico.

En mixturas con estreptomicina, se observó notable sinergismo bacteriostático y bactericida sobre el bacilo tuberculoso.

En un estudio clínico preliminar se observó que administración de grandes dosis de B 111 fué perfectamente tolerada.

RESUME

On a effectué la synthèse d'un groupe d'amides acides stéroïdes de la sulfone diaminodiphényl et on l'a expérimenté pour connaitre son activité chimiothérapique.

La sulfone 4-desoxycholylamino 4'-amino diphenyl (B 111)—un type reprèsentatif de ce nouveau groupe de composés—, fut tolérée en grandes quantités par les animaux d'expérimentation sans symptômes toxiques, administrée par voie buccale ou par voie intra-veineuse.

Les produits furent actifs *in vitro* sur des souches brutes et des souches de laboratoire de bacilles tuberculeux, et actifs *in vivo* sur la tuberculose animale expérimentale, en ce qui concerne la sulfone diamino-diphényl et autres, mais les dérivés de la DDS furent toxiques.

L'activité du B 111" fut imputable au composé non hydrolysé, selon les indications données par les comparaisons du spectre infra-rouge. La moitié stéroïde du composé semble agir à la fois comme un désintoxicant et comme un activant chimiothérapique.

Dans les associations avec la streptomycine, on observa une synergie avec des effets bactériostatiques et bactéricides remarquables sur le bacille tuberculeux.

Dans une étude clinique préliminaire, l'administration de doses élevées de B 111 fut parfaitement tolérée chez l'homme.

ZUSAMMENFASSUNG

Eine Serie von Steroidsäure-Amiden von Diamino-Diphenyl-Sulfon wurde synthetisiert und auf chemotherapeutische Aktivität geprüft.

4-desoxycholyamino 4'-amino diphenyl sulfon (B 111), eine repräsentatives Glied dieser neuen Gruppe von Substanzen, wurde in grossen Mengen von Versuchstieren vertragen ohne toxische Symptome bei oraler oder intravenöser Zufuhr.

Diese Substanz war aktiv in vitro auf "wilde" und laboratoriums-Stämme von Myco. tuberculosis und aktiv in vivo bei experimentieller Tiertuberkulose in demselben Grad wie Diamino-Diphenyl-Sulfon und andere, jedoch toxische Abkömmlinge von DDS.

Die Aktivität von B 111 war der nicht hydrolisierten Verbindung zuzuschreiben, wie aus Vergleichenden Infrarot-Spektren hervorging. Der Steroid-Anteil der Verbindung scheint gleichzeitig entgiftend und chemotherapeutisch aktivierend zu wirken.

In Mischungen mit Streptomycin wurde ein auffallender bakteriostatischer und bakterícider Effekt auf Myco. tuberculosis beobachtet.

Während einer vorläufigen klinischen Untersuchung wurde die Gabe von grossen Dosen von B 111 vom Menschen tadellos vertragen.

The Role of the Health Department in Tuberculosis Control

HOWARD E. SMITH, M.D., M.P.H., F.C.C.P.*
Austin, Texas

The Public Health Services' recent study of the unhospitalized tuberculosis patient is a shocking reminder of our failure to put into practice the control procedures currently available. Many of our committees continue to follow patterns of methods which have been known for long periods to *not* be the most yielding in results. We just do not use all the facts at hand. The recent survey by "Searchlight" has brought to light many inadequacies of community tuberculosis programs. One of the most glaring defects, revealed that these counties which did not have a health department knew little or nothing about the local tuberculosis problem. In general it may be stated that where the health department was lacking the services for follow-up, case finding, treatment, and supervision of the medically indigent tuberculosis case were also missing. Too many of our counties possess a part-time County Health Officer, as a rule untrained in modern public health practices, and without local resources to follow cases of reported tuberculosis. Infrequently is it possible for them to salvage any of the information on tuberculosis cases given them from official channels. Our major problem is to encourage these counties to provide health departments so that the people can receive needed services besides those that should be provided for tuberculosis cases and suspects.

The health department should be the core or hub of all health services in the County. It is true that few health departments can hope to provide all the health services needed. Even when all the health resources, and the various groups providing various health means have been marshalled and coordinated, deficiencies are likely to exist. The public's appetite for health services seems to be an insatiable one.

The availability of community health resources does not follow wishful thinking but from community organization. Community organization may be described as a method and a process by which needs are determined and resources mobilized and adjusted to meet those needs. The general aim of community organization is to bring about and maintain a progressively more effective adjustment between social welfare resources and social welfare needs. Only through concerted action can a community secure the services and facilities it desires. When the existing services have been surveyed and the needs determined, the health department should provide the leadership in effecting coordination Any organization—but usually it is one which is well established and recognized in the community—can initiate coordination.

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*Director, Division of Tuberculosis and Chronic Diseases, Texas State Department of Health.

To begin with, coordination is possible in a climate that makes provisions for it. Producing such a climate is largely a matter of education of the public and of professional workers. It is a matter of education on the practical values of coordination, to a point where individuals and organizations will do more than give lip service to the idea, will put forth the energy and will exercise the determination to make coordination work. An example of this thinking is the State Tuberculosis Coordinating Council.

Coordination needs financing. The care and supervision of tuberculosis patients requires both public and private funds. Those who administer funds must be alert to improved ways of using money both within their organization and jointly with other agencies in coordinated activities. It should be pointed out that many times, better services can be supplied with present funds if they were used to best advantage. The possibility of financial aid grows with the increase of knowledge about coordination.

The health department can provide counselling and referral services for those patients requiring continuing care, as well as offering direction and guidance to persons unfamiliar with the public, private health and welfare agencies' resources of the community. Keeping abreast of changing conditions would offer no challenge to the smaller counties.

One of the most valuable functions of a health department in tuberculosis control can reside in the maintenance of a case register. The case register should be kept up-to-date and can provide a useful tool and guide to the tuberculosis needs of the community. It should be possible to check the register and determine the status of every case which has been reported to the health department. Unless the register is used properly, it is not worth the effort to even provide one.

General services provided by the health department include the needed nursing services. These include supervision in the home for both the pre and post hospital patients as well as those which never leave the community. The general supervisory nursing services provided the patient will include education of the patient and family regarding the disease and in some instances, actual treatment as recommended by the physician. One of the greater contributions can be the locating of reported cases, suspects, and contacts and getting them under medical supervision and clinics for proper diagnosis. A nurse will also assist the patient, when the disease status so warrants, toward rehabilitation. The extensive use of effective drugs has changed the tuberculosis picture in the average patient from an acute communicable, highly fatal disease, to a chronic disease that is seldom fatal and communicable only periodically. One of the major results of drug treatment is prolonging the life of the patient. Since we do not know the full effects of drugs on the long-term condition of tuberculosis patients, these people will have to remain under observation and be checked periodically to determine their disease status. With more drugs being used in out-patient departments and more supervision being required, the long-term trend is to require more nursing services, and depending upon the volume of patients, those health departments having major tuberculosis programs will eventually reflect in the need for additional nurses. In the future the health department nurse can be expected to be called upon to play part in increasing the non-specific, but enchancing the resistance of the human body to the invading organisms. These measures will include improved standards of living, improved nutrition, and lessening the physical and emotional stresses of the patient.

Another major contribution of the health department can be year-round case findings. Periodic mass surveys have had their place but are no substitutes for continuous case finding. A good program can begin with tuberculin testing programs and examination of the positive reactors in areas of high infection prevalence. As the mortality rate decreases, there will come a time when mass x-ray surveys will no longer produce an economical yield. The case finding program, of necessity, will be focused on recognizing the infectious cases and breaking the chain of infection to those which are non-infected. More emphasis will be directed toward the epidemiological study of cases found, examining properly the contacts to locate new cases. More attention in the future will be likewise be given to those individuals who have already been infected and every effort will be made to prevent further development of disease. Many of our present cases may well represent breakdown from infection which occurred years ago. Other segments of population will need to be included in the case finding activities of the health department and should include people living in high prevalence areas, recipients from welfare assistance, and that population over 45 years of age.

As has already been stated, attention in the future will be crystallized upon breaking the chain of infection upon those individuals in the community who are infectious. The recalcitrant infectious case of tuberculosis will occupy a prominent place in the spot-light. When public education has been reached to the degree that each infectious case of tuberculosis and its potential can be appreciated, then the health officer will play a more vital part than he has in the past in the legal restraint of these infectious cases.

The health department or the regional health department laboratory provides the needed laboratory services for the indigent and medically indigent cases of tuberculosis. As more interest becomes focused on the control of the infectious case and with more cases to be evaluated from the use of new antimicrobial drugs, new demands on the laboratory services can be expected. Many of the laboratories now perform tests for bacterial indentification and resistance to the various drugs. As the importance of bacterial resistance becomes better appreciated in local clinics, it will be necessary to have more completely equipped laboratories.

Through the out-patient services provided by the health department, the opportunity is present for public health education of professional and non-professional personnel. Too often health departments have not assumed the responsibility which rests on their shoulders. Many of the smaller counties are in real need of training and developing interest of local physicians in assisting in the local tuberculosis program and modern treatment schedule of tuberculosis patients. The general practitioner can be expected to play an increasingly significant role in the home care of tuberculosis cases. With greater numbers of arrested cases in the community requiring long periods of observation and with lessened periods of hospital stay, the pattern of formal medical education should be coordinated to meet this trend.

One of the more valuable functions a health department can perform is a periodic, but regular evaluation of the tuberculosis program along, with the needed cost studies. Many of our counties would be amazed at the cost of finding a case of tuberculosis in the "teen" age group. Yet, year after year they continue to place major emphasis in the case finding program towards this captive population. Blindly we continue expending our efforts in less productive channels. This same force, if directed to the proper areas and proved population segments, could be definitely rewarding in the case yield. Our thinking in tuberculosis control should be directed to these vulnerable spots.

One of the commodities of a health department which is difficult to attach a dollar sign is leadership. Only through having personnel well trained in all of the various disciplines of public health can a county enjoy the full benefits of a good public health program. Well trained personnel of the type referred to are in short supply and are apparently expensive. Few realize, however, that they can ill afford to compromise with inferior health services. Good health for the citizens of a county is a purchasable asset. Through the Commissioner of Health's efforts, the best possible trained public health officers are being recruited that the market will supply. Every attempt is being made to recruit career-minded public health personnel and extend good health services to every citizen of the state.

The director of the local health department should always capitalize on the opportunity to provide leadership in the planning of the local tuberculosis control program. Since the health department will be involved in many of the aspects, it is imperative that the director offer medical leadership and bring in those medical agencies which will be involved in the program. Some local tuberculosis programs suffer because of the lack of medical planning. It also becomes the responsibility of the health department to develop and use its prestige. The personnel and activities of the department should always have the respect and confidence of the public. There should never be any question of the integrity of the health workers or the service of the department. The personnel of the department should never lose sight of the quality of humbleness and always regard themselves as a public servant contributing public service.

With public confidence regarding the elimination of tuberculosis as a health problem at its greatest height and with many people assuming a complacent attitude toward the disease, and in some instances agencies looking for new fields of endeavor, the health department has some responsibility in informing the public that the disease is not eradicated. We still have a problem in tuberculosis control.

Although it is not the direct responsibility of the health department, it should lend its prestige and confidence in recommending routine x-ray examinations of hospital admissions for unrecognized cases of tuberculosis. Some of the current figures indicate routine hospital admissions have 10 times the yield of ordinary mass x-ray surveys. The health department can at least place its stamp of approval on this recommended procedure.

Last but not least, the health department can, if personnel, funds and interest are present, play a contributing part toward further research regarding the disease. There is vital need for better methods of case findings, treatment and increasing the resistance of the infected and non-infected individual, not even to mention the need for better drugs, sharper tools and tests for diagnosing the disease, and means of providing better continuity of medical care.

SUMMARY

The County Health Department should serve as the hub of all health services and should offer leadership in coordinating and integrating the community health resources. It should offer counselling and referral services for persons unfamiliar with the public, private, health and welfare resources of the county.

The County Health Department usually maintains the case register of all known tuberculosis cases and provides nursing service in addition to year-round case finding activities. The control of recalcitrant tuberculosis cases usually is built around the local health department. Many local health departments provide needed laboratory tests, including sputum studies of suspected tuberculosis cases.

The Health Department should conduct periodic and regular evaluations of the local tuberculosis program and offer leadership in the planning of the control program. It has an obligation to provide information and the problem of tuberculosis to the public and should discourage complacency. Every health department should encourage routine chest x-ray films on all hospital admissions. If interest, funds and personnel permit, research studies should be conducted regarding the disease.

RESUMEN

El departamento de salubridad del condado debe servir como el eje de todos los servicios de salud y debe encabezar la coordinación e integración de los recursos de salubridad de esa comunidad. Debe ofrecer consejo y orientación para las personas no familiarizadas con los recursos de salubridad del condado ya sean públicos o privados.

El departamento de salubridad del condado generalmente mantiene el registro de casos conocidos de tuberculosis y provee de servicio de enfermeras además de la búsqueda de casos durante todo el año.

El control de los casos difíciles de conducir es una de sus actividades. Muchos departamentos de estetipo dan servicios de laboratorio, estudios de esputos de los casos sospechosos.

El servicio de salubridad debe llevar a cabo estimaciones regulares de los planes de lucha antituberculosa y ofrecer conducción en la planeación

de las tareas. Tiene la obligación de proporcionar información y presentar al púglico el problema así como evitar las complacencias. Todos estos servicios deben alentar los proyectos de roentgenfotografía de admisión a todos los hospitales.

Si hay interés y los fondos y el personal lo permiten, se deben hacer trabajos de investigación de la enfermedad.

ZUSAMMENFASSUNG

Das Kreisgesundheitsamt soll als Mittelpunkt dienen für alle Arten der Gesundheitspflege und soll die Leitung ermöglichen bei der Koordinierung und Vervollständigung der Hilfsmittel für das öffentliche Gesundheitsleben. Es soll beratende und bezügliche Dienste leisten für Personen, die nicht vertraut sind mit den öffentlichen, privaten, gesundheitlichen und fürsorgerischen Einrichtungen des Kreises.

Das Kreisgesundheitsamt führt gewöhnlich das laufende Register aller bekannter Tuberkulosefälle und sorgt für Pflegedienste zusätzlich zu den jährlichen Arbeiten zur Auffindung neuer Fälle. Die Aufsicht über uneinsichtige Tuberkulosefälle ist gewöhnlich mit dem örtlichen Gesundheitsamt verknüpft. Viele örtliche Gesundheitsabteilungen sorgen für die notwendigen Laboratoriumsuntersuchungen einschl. Sputumproben von verdächtigen Tuberkulosefällen.

Die Gesundheitsbehörde muss periodische und regelmässige Auswertungen der örtlichen Tuberkulosebekämpfungspläne durchführen und sich zur Leitung bei der Planung der Tuberkulosebekämpfung erbieten. Sie hat ein Verpflichtung zur Beschaffung von Informationen über das Tuberkuloseproblem für die Öffentlichkeit und hat die Selbstgefälligkeit zu bekämpfen. Jede Gesundheitsabteilung muss die planmässige Thorax-Röntgenaufnahme bei allen Krankenhauseinweisungen fördern. Wenn es das Interesse, die Geldmittel und das Personal zulassen, müssen Forschungsarbeiten hinsichtlich der Krankheit ausgeführt werden.

Pre- and Para-Medications in Bronchoscopy*
The Concept of "Broncho-Softening"

R. BENDA, M.D., P. BENDA, M.D., E. ORINSTEIN, M.D., and P. DELIGNÉ, M.D.
Paris, France

It has become easy to explore the respiratory tract—the necessary instruments are greatly improved and easy to manipulate, and the use of local anesthesia is well established. Medication which, as a sedative, combines morphine and atropine, the anti-secretive effect of which is excellent, is satisfactory to bronchologists in a great majority of cases, so that few attempts have been made to modify the technique generally used.

Nevertheless, there are some difficult bronchoscopies which are not to say "impossible." Often the difficulties are caused by the patient's fears, whether at the first trial or at a series of examinations; or they may result from buccal-mandibular malformation (for example, where the face has been mutilated). Once the glottal passage has been traversed, apart from a stricture of organic origin, one may encounter bronchial spasm, or sometimes a curve to the left more accentuated than usual.

To improve the technique and, therefore, the results of endoscopy, one would have to reinforce or perfect the means of:

1. Dissipating the patient's fears.
2. Facilitating the tracheal tube insertion.
3. Eliminating any eventual bronchial spasm and even extending the passage of the tube beyond the usual limits.

Pre-medication would be affected mostly by the first two indications, and para-medication by the third. But, indeed, several of these indications overlap and it is only for purposes of classification that we list them chronologically.

I. PRE-MEDICATION

Out of the many drugs we explored with a view to their effective use prior to intubation, only two were kept: diethazine and an anesthetic steroid (Viadril).

1. *Diethazine* (or 2987 R.P.)**

For the morphine-atropine pre-medication used currently we substitute a combination of diethazine with atropine.[1]

Let us recall briefly the properties of 2987 R.P. This product has been used in the treatment of Parkinsonian syndromes. It is a salt of diethylamino-2′-ethyl N-dibenzopara-thiazine.

It results from the condensation of a salt derived from diethylamino-ethanol which enters into the composition of numerous medicaments (pro-

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Centre de Phtisiologie et de Pneumologie de l'Hopital Beaujon.

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**Latibon (Bayer).

caine, certain spasmolytics and sympatholitics) and of an elixir of thiodiphenyl-amine.

In the parasympathetic ganglions, 2987 R.P. causes a vagal paralysis without the effect of the acetylcholine being appreciably modified.

In the sympathetic ganglions, it produces a similar paralysis which manifests itself, for example, by its antagonism to the tension-causing effects of nicotine.

It also opposes adrenalin secretion of the adrenal medulla following the stimulation of the splanchnic nerves provoked by asphyxiation.

It also exercises a central analgesic action.

Pre-medication by diethazine aims at preventing, or diminishing, bronchospasm, an action resulting from the anti-nicotinic properties of 2987 R.P. In fact, experience has shown us further results: not only does diethazine simplify intubation, but it often permits attaining unusual depths in the bronchial tree without forcing the basal bronchi (as is shown by a cinematographic sequence showing an air cyst, distal and invisible on x-ray films, either standard or tomographical). This is the first demonstration of the "bronchial-softening" effect.

The *dose* of diethazine, injected *intramuscularly* a quarter of an hour before the local anesthetic, is the same for all patients: 250 mg. dissolved in 5 ml. of physiological saline, mixed with 1.0 mg. of atropine sulphate in the same syringe.

The product has only one drawback, and that a minor one. The day after the injection it causes a rather severe pain *in situ*, which may persist for two or three days. A greater dilution in physiological saline and dividing the total dose into two injections, one on the right, and the other on the left, corrects this drawback to a certain extent.

2. *Anesthetic steroid* (P 55 or Viadril)

Even though diethazine produces consistently satisfactory effects by a simple method, there remains, nevertheless, a certain group of patients whose emotions or tenseness risk upsetting the endoscopic exploration. For them we can use an anesthetic steroid, the succinate of 21-hydroxypregnandione, investigated by Laubach and his collaborators.

This product is a white crystalline powder, soluble in water, with a molecular weight of 432. In solution, its pH is 8.5 to 9.8. It has no toxic effect, and does not cause retention of sodium.

In weak doses it causes simple hypnosis. In strong doses (for example, 1.5 gm.) it produces anesthesia, which begins after five minutes and may continue for a long time.

Bronchoscopy usually requires neither deep nor prolonged anesthesia. In any particular patient, the use of P 55, as pre-medication, is justified by the state of calmness it produces and by its quasi-selective action on the striated glottal muscle, facilitating greatly the tracheal tube insertion.

It is on this account that we have been led *to modify the doses injected in general anesthesia* by the team from the University of California, *and even the technique of injection.*[2] Two hours before the endoscopic exploration, we start an intravenous infusion into an antecubital vein (using a

TABLE I

Names	Pre-medication (Diéthazine 250 mg. + Atropine 1 mg.	Para-medication (Succinylcholine 2 mg. + Lignocaine 5 mg.)	Broncho-softening Effect	Comments
Dor. . .	I.M. injection		+	
Mar. . .	id.		+	
Chat. . .	id.		++	
Gol. . .	id.		++	
Tho. . .	id.		+	sleep during the procedure
Cai. . .	id.		0	organic narrowing
Azé. . .	id.		0	organic narrowing
El. H. . .	id. (+ previous Viadril)		++	
Dur. . .	id. (+ previous Viadril)		+	
Pou. . .	id. (+ previous Viadril)		+	
Le G. . .	id.	I.V. injection	++	visibility of the division of Nelson bronchus
Thom. . .	id.	id.	++	
Mart. . .	id.	id.	++	left curve ++ passed over
Le F. . .	id.	id.	++	left curve + passed over
Ker. . .	id.	id.	+	
Tid. . .	id.	id.	++	
Der A. . .	id.	id.	0	organic narrowing
Rol. . .	id.	id.	++	spasmodic narrowing
Aug. . .	id.	id.	++	
Blo. . .	id.	id.	++	
Gic. . .	id.	id.	++	
Rem. . .	id.	id.	++	
Yah. . .	id.	id.	++	
Bou. . .	id.	id.	++	
Fil. . .	id.	id.	++	
Zac. . .	id.	id.	++	spasmodic narrowing
Tab. ..	id. (+ previous Viadril)	id.	+	no local anesthetics
Ves. . .	id. (+ previous Viadril)	id.	+	
Luc. . .	id. (+ previous Viadril)	id.	+	
Hel. . .	id. (+ previous Viadril)	id.	++	

20 gauge needle) of 250 ml. physiological saline to which is added 5.0 mg. of Viadril per kilogram of body weight. The speed of infusion is regulated to last for two hours.

From this, one does not obtain a true anesthetic effect, but before long a complete euphoria is established, or a total indifference to the procedure. At completion of the injection, the subject is capable of getting up unaided, and is ready for the laryngo-tracheal anesthesia. From here on the procedure becomes simple and, once the bronchoscopy is concluded, the patient quickly returns to normal activity.

This technique of preliminary intravenous infusion avoids the salivary hypersecretion, which the rapid intravenous injection of the anesthetic steroid provokes. The atropine, always concurrently used, diminishes still further the risk of sialorrhea.

As this technique is not as simple as the first, we need to use P 55 only in the following cases:

1. Anterior failure of the glottal passage.
2. Very frightened or agitated subjects.
3. Bucco-mandibular malformations.*

Pre-medication, then, by diethazine alone, or by diethazine and Viadril, permits one to obtain a certain "broncho-softening" effect with the first drug, and quieting effects, accompanied often by an actual glottal gaping, with the second.

The "broncho-softening" effect is enhanced by para-medication, which we accomplish with a synthetic curare-like compound.

II. PARA-MEDICATION

The first investigations of two of the authors, with Paillas and Maroger,[3] were concentrated on the natural alkaloid of curare (d-tubocurarine), the particular action of which, on the bronchial tonicity, has been described precisely under the name of "*broncho-softening effect.*" We have abandoned it recently in favor of *diiodide of succinylcholine,*[4] one of the most remarkable among the numerous synthetic curare-like compounds proposed in recent years, by reason of its transitory action, which makes it especially easy to handle. Bovet and his collaborators[5] have described this product. Its brief action appears to be connected with its rapid hydrolysis by the plasma cholinesterase, whereas most of the curare-like compounds are essentially excreted by the kidneys.

With succinylcholine one finds again the *broncho-softening effect* of d-tubocurarine. As we stressed at the very beginning of our studies on the use of curare in bronchoscopy,[3] "the bronchi become soft, extraordinarily flaccid; it almost seems as if they open up before the bronchoscope; they permit an easy progression of the tube, which reaches the terminal branches of the bronchial division and sometimes even goes into them. The leftward bronchial curve is easily overcome." The only cases in which observations of this extent are not possible are in the *organic* stenoses.

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*One should carefully estimate any eventual risk in a few clinical cases, such as marked respiratory insufficiencies or severe vegetative disturbances (asthma).

In other words, this broncho-softening effect may be appreciated:

1. By the facility which one experiences, once the scope has been introduced into the respiratory tract, in moving the instrument back and forth inside the bronchial lumen.

2. By the possibility, when encountering a bronchial zone which is in spasm, of traversing it, once an injection of this product is given.

To sum up, such "broncho-softening" would not be appreciated without the presence of the tube in the bronchus; it is only noted by mediate tactile perception. One can see how this distinguishes it from bronchodilatation (Figure 1).

The interest in these facts appears to us twofold:

1. From the doctrinal point of view, they show the *action of curare on smooth muscle,* by the probable intermediary of the neuro-vegetative system.

Years ago Vulpian and, more recently, Langley pointed out that curare blocks the synaptic ganglionic transmission. Luco and Mesa utilized the pupillary response of the cat and the contraction of the nictating membrane, and demonstrated the blocking of cholinergic synapses. MacIntyre concedes that all the tissues where acetylcholine intervenes are susceptible to curare in varying degrees.

Clinically, Gross and Cullen point out the diminution of intestinal peristalsis; Batelli, and Switski, that of contractions of the stomach; and

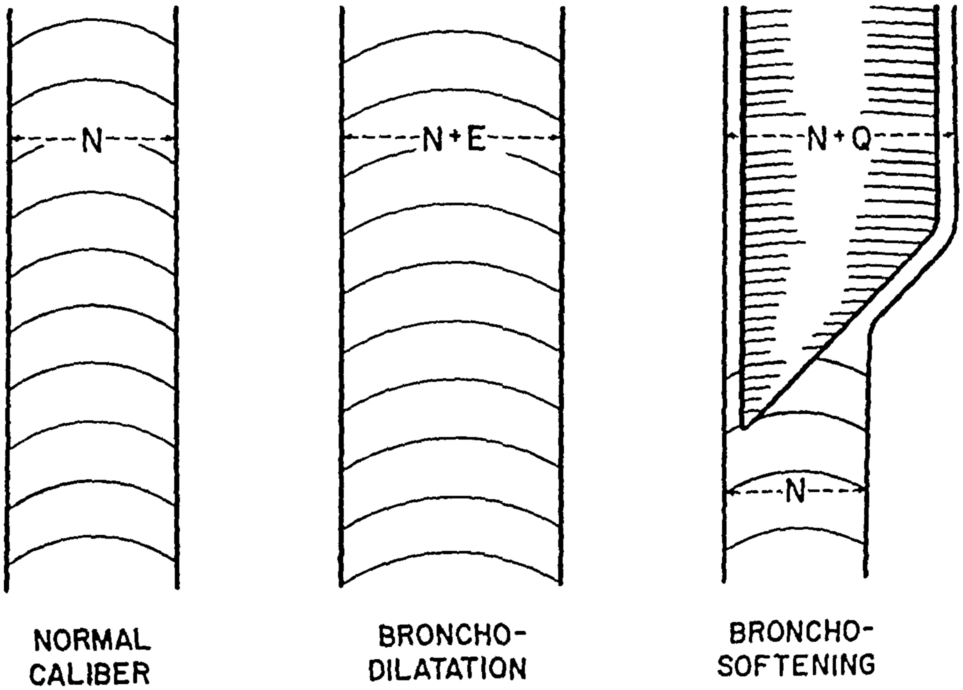

FIGURE 1: The "broncho-softening" would not be apparent without the presence of the tube in the bronchus. N = Normal. N + E (epsilon, ancient Greek letter meaning a very small quantity) = Moderate expansion of the bronchus from broncho-dilating agent alone. N + Q = More extensive expansion of the bronchial lumen. The bronchial wall is now more expansible when the bronchoscope is inserted and is capable of greater dilatation.

Cornet has verified for us, in the course of gastroscopies, the pyloric atony due to curare.

2. From the practical point of view—the one which interests us especially here—the same circumstances permit an *extension of the field of exploration of the bronchoscope,* revealing sometimes a lesion inaccessible with standard technique, and even allowing a biopsy otherwise impracticable.

In our first trials, the *doses of succinylcholine,* administered intravenously, varied from 5 to 30 mg. A broncho-softening effect, remarkable by its constancy and by its intensity, showed itself even in weak doses, smaller than 0.2 mg./kg. In such small doses, however, where the peripheral muscular relaxation is slight or even absent, one could still observe, in certain subjects, a short period of apnea. Although such a reaction could give no unfavorable results, it did stimulate us to seek by means of various substances (chlorpromazine, in particular), with the object of diminishing still more the dose of the active product to be injected.

At the present time, our preferences are turning to a derivative of acetanilid, lignocaine (or xylocaine), itself efficacious in small doses. Thus the mixture in the same syringe of 2 mg. of succinylcholine and 5 mg. of xylocaine (in a solution of 1 per cent) represents a uniform dosage which, introduced intravenously, obtains an undeniable broncho-softening effect, while keeping well below the apnea dose.

The curare-like compound must be ready, together with xylocaine, before starting the bronchoscopy, but held in reserve and only used when necessary. It will prove efficacious where the pre-medication has not sufficed.

We are reporting, in Table I, 30 unselected cases of endoscopic examinations done recently, which illustrate the possibilities and the limits of the means employed. One can see, as we stated at the beginning of this paper, that pre- and para-medications have overlapping indications. Thus, diethazine has broncho-softening effects; likewise it is a central sedative, but the broncho-softening effects are more marked with succinylcholine. On the other hand, the anesthetic steroid, even though it has no broncho-softening effect, acts on the striated glottal muscle and facilitates tube insertion. In this respect, its action completes, on the laryngeal level, the broncho-softening effects of curare-like compounds and of diethazine at the level of the smooth bronchial muscle. It is, besides, a powerful sedative, with hypnotic effect.

Finally, we propose the following schema for pre- and para-medication in bronchoscopy:

a) *In non-nervous subjects*

1. The injection of diethazine-atropine preceding by a quarter of an hour the beginning of:
2. Local anesthesia.
3. When necessary (for example, a difficult leftward curve, spasm, etc.) succinylcholine, in very small, non-apnea producing doses, combined with xylocaine, injected intravenously.

b) *In nervous subjects*

During the two hours which precede the bronchoscopy, an intravenous infusion of P 55 should be administered, designed solely to facilitate the tube insertion.

Following this infusion of P 55, one returns to the above schema (a): that is, the preparation by diethazine-atropine; and subsequently, when necessary, intravenous injection of a combination of succinylcholine and xylocaine in very small doses.

SUMMARY

With a view to improving the technique and, consequently, the results of bronchial endoscopy, the authors have systematically employed, as *premedication, diethazine* combined with atropine; and in some cases, an *anesthetic steroid (P 55)*. A certain "broncho-softening effect" is obtained with the first drug; a tranquilizing effect, accompanied by a veritable glottal gaping, with the second.

But the broncho-softening effect is, first and foremost, linked with *paramedication,* which consists of a small dose of a synthetic curare-like compound, *diiodide of succinylcholine,* the action of which is potentiated by the addition of an equally small dose of lignocaine.

The concept of "broncho-softening" under the influence of succinylcholine, in particular, permits an extension of the field of exploration of the bronchoscope, revealing sometimes a lesion which would be inaccessible with standard technique, and even allowing an otherwise impracticable biopsy.

Addendum

Recently, we employed *Chlorpromazine* as a premedication: 25 mg., dissolved in 5 ml. of physiological saline, injected intramuscularly 20 minutes before the local anesthesia.

This drug had favorable effects: we noted its strong tranquilizing properties. Also its anti-secretive power was evident on endoscopic examination of the tracheobronchial tree, although no atropine had been given.

RESUMEN

Con la mira de mejorar la técnica y consecuentemente los resultados de endoscopía bronquial, los autores han empleado sistemáticamente la *premedicación* por la *Diethazine* combinada con atropina; y en algunos casos un *esteroide anestésico (P-55)*.

Cierto "efecto de ablandamiento bronquial" se obtiene con la primera droga; un afecto tranquilizador, acompañado de una verdadera relajación glótica con la segunda.

Pero el efecto de ablandamiento bronquial es primero y principalmente ligado a la *paramedicación* que consiste en una pequeña dosis de un compuesto sintético análogo al curare, *diyoduro de succinilcolina,* cuya acción es potencializada por el agregado de una dosis igualmente pequeña de lignocaína.

El concepto de "ablandamiento bronquial" bajo la influencia de la succinilcolina en particular, permite una extensión en el campo de la exploración de la broncoscopia revelando a veces una lesión que sería inaccesible

con la técnica común y permitiendo aún una biopsia de otra manera impracticable.

RESUME

En vue d'améliorer la technique et, partant, les résultats de l'endoscopie bronchique, les auteurs ont utilisé, *à titre de prémédication,* systématiquement: *la diéthazine* associée à l'atropine; éventuellement: *un stéroïde anesthésique* (*le P 55*). Un certain effet "broncho-émollient" est obtenu avec la première drogue; un effect apaisant, s'accompagnant d'une véritable béance glottique, avec la seconde.

Mais l'effet broncho-émollient est surtout lié *à la para-médication* qu'ils font avec de très faibles doses d'un curarisant de synthèse, *le diiodure de succinylcholine* (dont l'action est potentialisée par l'adjonction de doses également très faibles de lignocaïne).

La notion de "broncho-émollience" sous l'influence de la succinylcholine, en particulier, permet d'étendre le champ d'exploration du bronchoscope, de déceler parfois une lésion inaccessible avec la technique standard et même d'exécuter une biopsie autrement impraticable.

ZUSAMMENFASSUNG

Im Hinblick auf eine Verbesserung der Technik und damit zugleich der Ergebnisse der bronchialen Endoskopie haben die Verfasser systematisch als *Praemedikation Diethazin* in Verbindung mit Atropin angewandt und bei einigen Fällen ein anaesthesierendes Steroid (P-55). Ein gewisser "bronchuserweichender Effekt" wird mit dem erstgennanten Mittel erreicht; ein beruhigender Effekt, begleitet von einem förmlichen Klaffen der Stimmritze, mit dem zweiten.

Aber der Bronchuserweichende Effekt ist in erster Linie geknüpft an eine Paramedikation, bestehend aus einer kleinen Dosis ines synthetischen kurare-artigen Stoffes, dem Dijodid dem *Succinylcholin,* dessen Wirkung potenziert wird durch den Zusatz einer gleichfalls kleinen Dosis von Lignocain.

Die Vorstellung der "Bronchus-Erweichung" unter dem Einfluss von Succinylcholin erlaubt in besonderem eine Ausdehung des Untersuchungsgebietes für das Bronchoskop und zeigt mitunter einen Herd, der mit der Standardtechnik unzugänglich wäre, und ermöglicht sogar eine auf andere Weise undurchführbare Biopsie.

REFERENCES

1 Benda, R., Orinstein, E., Deligné, P. and Benda, Ph.: "Troisième série de recherches sur les broncho-émollients. Action de la diéthazine (2987 R.P.)," *Bull. et mém. Soc. méd. d. hop. de Paris,* no. 23-24, p. 905, 1955.
2 Benda, R., Orinstein, E. and Nataf, R.: "Sur l'emploi d'un stéroide anesthésique en pratique bronchologique," *Bull. et mém. Soc. méd. d. hop. de Paris,* no. 12-13, p. 377, 1956.
3 Benda, R., Benda, Ph., Maroger, M. and Paillas, J.: "Effet broncho-émollient du curare. Son utilisation en bronchoscopie," *Bull. et mém. Soc. méd. d. hop. de Paris,* no. 17-18, p. 385, 1947.
4 Benda, R., Benda, Ph., Orinstein, E. and Deligné, P.: "Deuxième série de recherches sur les broncho-émollients. Effet de la succinylcholine," *Bull. et mém. Soc. méd. d. hop. de Paris,* no. 24-25, p. 371, 1954.
5 Bovet, D., Bovet-Nitti, F., Guarino, S., Longo, V. and Fusco, R.: *Arch. Internat. de pharmacodyn.,* 88:1, 1951.

Pulmonary Metastasis from Occult Primary Sites Resembling Bronchogenic Carcinoma*

BENJAMIN E. GREENBERG, M.D.** and JOSEPH M. YOUNG, M.D.†
Memphis, Tennessee

During the six year period from 1950 to 1956 radiation therapy was given to almost 300 patients with thoracic lesions diagnosed as bronchogenic carcinoma. The cases fell into the following groups; explored but not resectable, resected but with involved nodes remaining, inoperable and surgery refused. Six cases[5] with histologic confirmation of malignant tumor prior to radiation, which were considered to be compatible with bronchogenic carcinoma and so treated, at autopsy proved to be metastasis from a silent extrathoracic primary tumor. The clinical, radiological and pathologic considerations of these cases will be presented.

A diagnosis of metastasis to the lungs is usually accurate with solitary or multiple tumors when the primary source is known.[5] When the pulmonary nodule is solitary and no primary source can be located the diagnosis of metastasis may be impossible without thoracotomy and histologic examination. Solitary metastasis to the lungs, and for that matter elsewhere, is not common,[7, 23] but is known to arise from many primary tumors particularly of the kidneys. The much higher frequency of primary carcinoma of the lung in the older age groups accounts for this diagnosis being favored rather than suspecting a secondary tumor.

The lungs act as a primary filter for tumor emboli released into the systemic veins or thoracic duct and may secondarily receive tumor emboli from the portal system by way of the liver. It is not surprising that Turner and Jaffee[29] in reviewing a large series of metastatic lung tumors found that 50 per cent of tumors of neuromuscular and skeletal origin metastasized to the lungs as well as the same percentage of glandular and hematopoietic tumors. Of the following sites of primary tumors, 25 per cent metastasized to the lungs; urinary and male genital organs, female genital organs, gastrointestinal tract and respiratory system. Only 10 per cent of oral cavity tumors metastasized to the lungs. Generally speaking, about 30 per cent of all fatal cases of malignant tumors will have pulmonary metastases. Russo and Cavanaugh[26] demonstrated an increasing incidence of metastatic lung tumors after 40 years of age with the highest in the 60 year and over group. This is not unlike the age incidence of bronchogenic carcinoma.

Tumors reaching the lungs through the circulation may give rise to lesions that remain asymptomatic for varying time intervals depending upon such factors as rate of growth, number of nodules and proximity to bronchi. Eventually, there may appear symptoms of dyspnea, cough,

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**Chief of Radiology Service.
†Chief of Laboratory Service.
*From the Radiology Service and Laboratory Service, Veterans Administration Hospital, Kennedy Division.

sputum, weight loss, chest pain and hemoptysis. Metastasis directly through lymphatics to the hilar and mediastinal lymph nodes with subsequent bronchial compression or invasion is infrequent. Even less frequent is metastasis to the wall of the bronchus by way of the pulmonary or bronchial arteries.[21, 33] It is in these uncommon instances that the clinical and radiographic features are indistinguishable from primary bronchogenic carcinoma. Hemoptysis, atelectasis, hilar and mediastinal lymph node enlargement occur in both conditions; even the tumor may be visible to the bronchoscopist with biopsies positive for tumor.[15] Cytology studies of bronchial secretions may occasionally reveal tumor cells from a metastatic lesion. Metastatic tumor to hilar nodes may infiltrate the lung and ulcerate a bronchus as stated, while a peripheral secondary pulmonary nodule may yield metastasis to adjacent nodes[33] resulting in a radiographic appearance identical with that of bronchogenic carcinoma. There have been such occurrences in cases of carcinoma of the breast, kidney, colon and testes.[2]

In a significant percentage of cases the pathologist while recognizing that a malignant tumor exists will be unable to state the tissue of origin from the study of biopsy sections.[19] This may be due to the anaplasia of the secondary tumors and the not infrequent variations of the histologic appearance in different parts of a tumor. The limited biopsy specimen may not be sufficiently representative of the tumor as a whole. Furthermore, congestion, inflammation and necrosis may also modify the histologic appearance of the tumor so that even a thorough study of the complete surgical specimen may not permit a definite diagnosis.[33] Kirklin and his associates[22] in a restudy of the cell types in 844 cases of bronchogenic

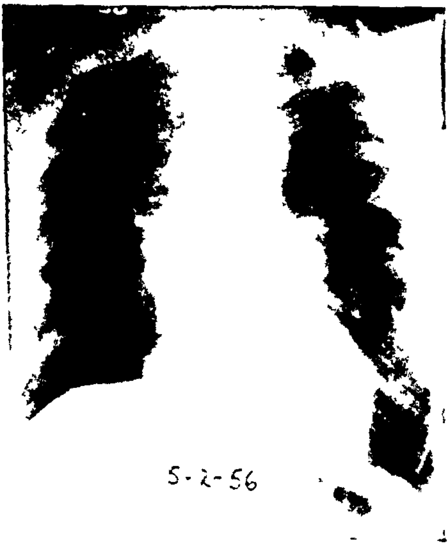

FIGURE 1

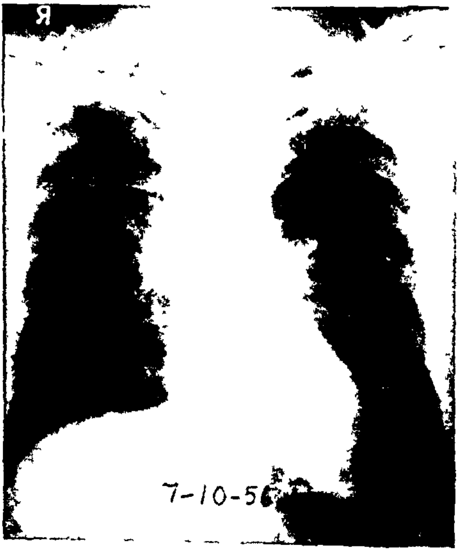

FIGURE 2

Figure 1 (Case 1): Primary tumor in pancreas. Mass in right hilum and right superior mediastinum with contraction of right upper lobe.—*Figure 2* (Case 1): Marked tumor regression one month after radiation therapy.

carcinoma noted the difficulty in differentiating some adenocarcinomas of the lung from metastatic tumors. This was also the experience of Russo and Cavanaugh.[26]

There have been a number of case reports of lung lesions appearing to be bronchogenic carcinoma but which proved to be metastatic from primary tumors removed surgically up to 20 or more years previously.[4, 6, 8, 9, 11, 12, 14, 23, 25, 27, 28, 30] Such primary lesions have included carcinomas of the kidney, colon, thyroid, breast, uterus and ovary, sarcoma of bone, melanoma of skin, testicular tumors and fibrosarcoma. Current opinion favors the resection of solitary lung nodules even if a secondary tumor were suspected[5] because of a history of a previous primary tumor. The solitary nodule may prove to be a benign tumor, granuloma, or even a new primary malignancy in the lung.

We now come to the consideration of lung lesions which resemble bronchogenic carcinoma without a history of a previously resected malignant tumor and which later proved to be metastasis from a clinically silent extrathoracic primary site. A limited search of the literature produced 14 well documented cases[1, 13, 17, 20, 21, 24, 31, 32, 34] which fell into this group but in only six was the primary site named. They were as follows, kidney, two cases; pancreas, stomach, testes, gallbladder, 1 case each and primary site not stated, eight cases. The present report adds six additional cases—pancreas, three, prostate, two, and kidney, one.

Case Reports

Case 1: L. R. J. Primary Tumor in Pancrease. This 64 year old white man had cough, weight loss and superior mediastinal obstruction. Chest film (Fig. 1) revealed elevation of right diaphragm, right superior mediastinal mass and right upper lobe contraction.

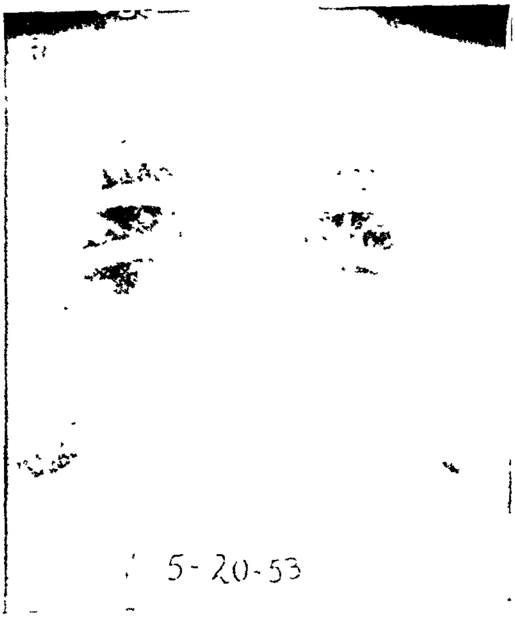

FIGURE 3

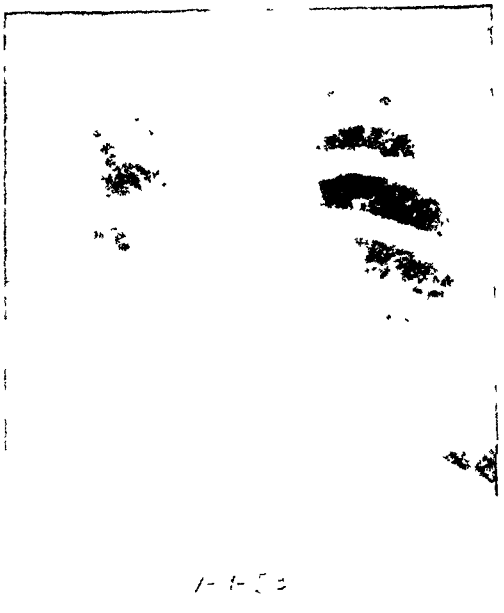

FIGURE 4

Figure 3 (Case 2): Primary tumor in pancreas. Lobulated right hilal mass with adjacent peripheral mass prior to thoracotomy.—*Figure 4* (Case 2): Regression of right lung masses after radiation therapy. Pleural reaction at right base related to surgery.

Bronchoscopy demonstrated corrugated appearance of right upper lobe bronchus but biopsy was negative. Right supraclavicular node biopsy reported as anaplastic carcinoma, possibly adenocarcinoma. He received radiation therapy for 6647r tumor dose in 31 days with no change in x-ray film appearance at completion of therapy, but marked symptomatic improvement. A month after therapy (Fig. 2) there was evidence of some tumor regression. He died five months from beginning of radiation.

Autopsy revealed tumor in hilar and mediastinal nodes compressing trachea, esophagus and superior vena cava. The right upper lobe bronchus was compressed by a 4 cm. mass. Microscopic examination demonstrated invasion of the bronchus by tumor. A 3 x 4 cm. mass was found in the tail of the pancreas. The final diagnosis was adenocarcinoma of the pancreas with metastasis to lungs, lymph nodes and elsewhere.

Case 2: S. S. Primary Tumor in Pancreas. This 56 year old man was admitted for investigation of a chest lesion discovered by a mobile chest unit. All studies including a gastrointestinal series and sputa were negative. A chest roentgenogram (Fig. 3) prior to thoracotomy demonstrated a lobulated right hilal mass with an adjacent parenchymal nodule. At surgery the lesion was considered non-resectable because of involved mediastinal nodes. One node removed for biopsy was reported as anaplastic metastatic tumor probably from bronchogenic carcinoma.

He received radiation therapy for a tumor dose of 6646r in 34 days. When treatment was finished (Fig. 4) there was almost complete tumor regression.

He got along well for nine months when he was readmitted with signs of myocardial infarction. He died June 9, 1954, one year from beginning of radiation. Autopsy revealed no evidence of tumor in either lung. The body and tail of the pancreas was completely replaced by tumor and contained a 5 cm. pseudocyst. The diagnosis was carcinoma of pancreas with metastasis to liver and abdominal lymph nodes.

Case 3: C. I. C. Primary Tumor in Pancreas. This 47 year old white man was admitted with left chest pain and cough. He had subtotal gastric resection for chronic duodenal ulcer three years previously. A chest roentgenogram revealed a left hilum mass with infiltration and atelectasis of left lower lobe (Fig. 5). On bronchoscopy an endobronchial lesion was found but biopsy was negative for tumor. A gastrointestinal series revealed the gastroenterostomy to be functioning normally. Sputum studies were negative.

He was referred for radiation therapy without an established diagnosis but clinically considered as inoperable bronchogenic carcinoma. After a tumor dose of 6000r in 40 days there was complete clearing of the left lung lesions (Fig. 6). The left lung in-

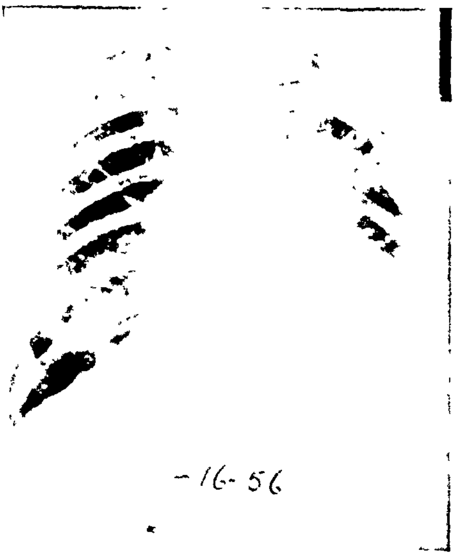

FIGURE 5

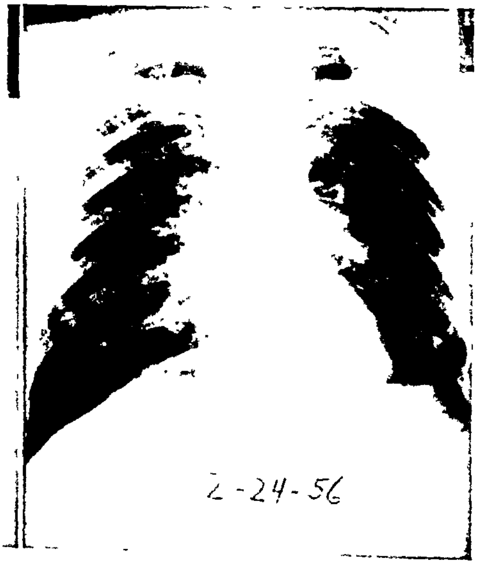

FIGURE 6

Figure 5 (Case 3): Primary tumor in pancreas. Left hilal mass with lower lobe atelectasis and pneumonitis.—*Figure 6* (Case 3): Regression of hilal mass and reaeration of left lower lobe after radiation therapy.

filtrations subsequently recurred with the development of a lung abscess. He died four months after beginning of radiation.

Autopsy demonstrated a large left lower lobe abscess, an 8 x 10 cm. mass in the left upper quadrant of the abdomen with extension to the adjacent stomach, colon and kidney. The mass replaced the tail of the pancreas. The final diagnosis was anaplastic carcinoma of the tail of the pancreas with extension to neighboring organs and metastases to left lung and elsewhere.

Case 4: W. S. Primary Tumor in Prostate. This 57 year old colored man had progressive dysphagia, epigastric pain and weight loss. A chest roentgenogram revealed a large mediastinal mass and a right lung peripheral nodule. Bronchoscopy revealed a mass in the right main stem bronchus. Biopsy was reported as oat-cell bronchogenic carcinoma.

He was referred for radiation therapy. Chest x-ray film (Fig. 7) showed a large mediastinal mass bulging into the right hilum region and a right lung nodule at the level of the fifth anterior rib. He received a tumor dose of 3135r in 20 days without effect. Treatment was interrupted because of his rapidly deteriorating condition. He died one month from beginning of radiation.

Autopsy revealed a mass involving the right hilum and mediastinum. The mass surrounded the right main bronchus and demonstrated on histologic section that tumor extended to the mucosa (Fig. 8). The prostate revealed a 2.5 cm. nodule adjacent to the symphysis. On cut section the prostate was almost entirely replaced by tumor. The final diagnosis was carcinoma of the prostate with metastasis to lung, lymph nodes and elsewhere.

Case 5: J. H. P. Primary Tumor in Prostate. A 56 year old white man was found to have a peripheral pulmonary nodule (Fig. 9) at an admission for a herniorrhaphy. He refused thoracotomy at first but accepted it five months later.

The right upper lobe lesion became slightly larger during this interval. At thoracotomy a right upper lobe mass was confirmed but because of tumor in hilar nodes, identified on frozen section, no resection was done. He was given radiation therapy for a tumor dose of 6000r in 42 days with some decrease in size of the mass. His course was slowly downhill with death occurring 18 months after beginning of radiation.

Autopsy demonstrated bilateral metastatic pulmonary tumor nodules; no endobronchial tumor could be identified. The prostate was grossly normal but histologic examination revealed carcinoma. The final diagnosis was carcinoma of the prostate with metastasis to nodes, lungs and elsewhere.

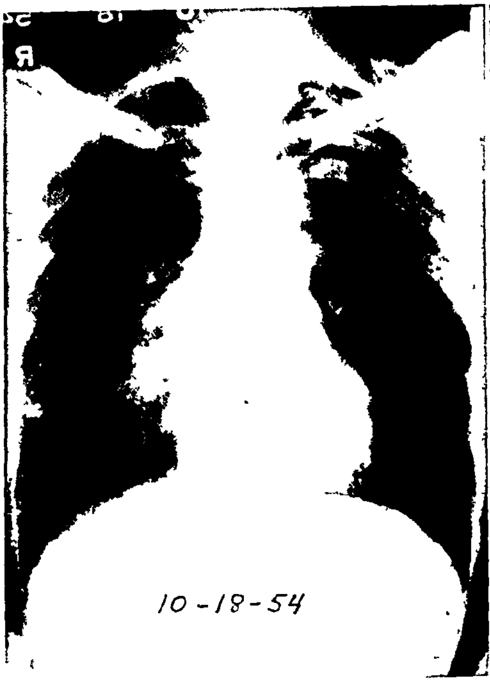

FIGURE 7

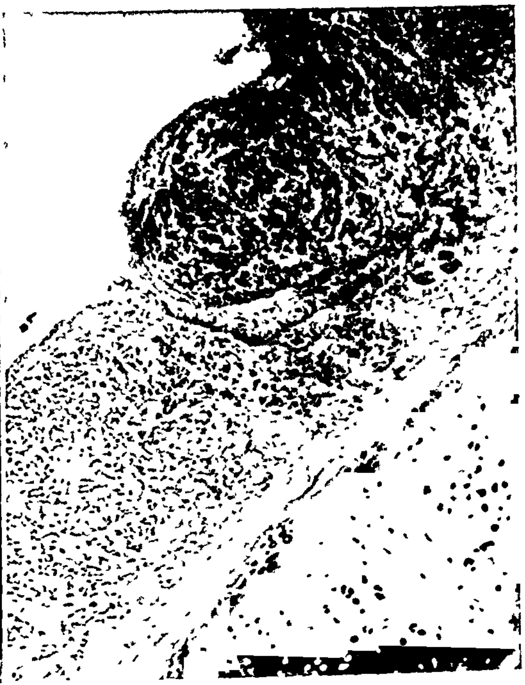

FIGURE 8

Figure 7 (Case 4): Primary tumor in prostate. Mediastinal and right hilal mass as well as a peripheral nodule at the level of the right 5th anterior rib.—*Figure 8* (Case 4): Histologic section of bronchus demonstrating extensive tumor invasion of sub-mucosa.

Case 6: J. L. R. Primary Tumor in Kidney. This 34 year old colored male was admitted October 27, 1955 with an acute respiratory infection. He had had frequent such episodes for the past eight years. Chest roentgenogram on admission (Fig. 10) demonstrated cystic disease involving the upper half of the right lung and left apex. Several fluid levels are noted within the cysts. He became symptom free with antibiotics. Sputum cultures were negative for tubercle bacilli and fungi. Urinalysis was negative. Film two months later (Fig. 11) showed a nodular density near upper part of the right hilum and apex of right lung with a fluid level in the apex. A clinical diagnosis of infected cystic disease with possible neoplasm was made and right upper lobectomy was done January 16, 1956. The surgical specimen showed multiple cysts with the apical cyst containing a 5 cm. mass. Histological examination demonstrated granulomatous tissue as well as anaplastic carcinoma. The diagnosis was bronchogenic carcinoma and granulomatous disease.

He received radiation post-operatively for a tumor dose of 6615r in 30 days. He was readmitted three months after radiation with cough and bilateral lung nodules revealed on x-ray film. Urinalysis was negative at first on this admission but later showed microscopic hematuria. An intravenous pylegram showed failure of filling of left lower and middle calyces consistent with renal tumor.

He died five months from beginning of radiation. Autopsy showed the left kidney almost replaced by tumor. The final diagnosis was carcinoma of kidney with metastasis to liver and lungs.

Comments

Pancreatic carcinoma commonly spreads to regional nodes and to the liver. Blood-borne metastasis occurs in 20 per cent of fatal cases.[33] Diagnosis of carcinoma of the tail of the pancreas is rarely made prior to laparotomy or autopsy and would escape detection in the absence of symptoms.

Carcinoma of the prostate showed an incidence of pulmonary metastasis of 38 per cent in cases coming to autopsy,[10] but only 8.6 per cent showed x-ray film evidence of secondary lung tumors.[16] This indicates that detectable lung metastasis in carcinoma of the prostate is usually a late, near terminal, manifestation. Russo and Cavanaugh[26] found no case of metastasis to the lungs from carcinoma of the prostate in their study of 105 metastatic lung lesions.

Lung metastasis is frequent from carcinoma of the kidney, as high as 75 per cent in fatal cases.[33] This high incidence is to be expected since metastasis in usually by way of the blood stream. Occasionally, mediastinal and hilar nodes may be involved. The tendency for solitary lung metastasis from carcinoma of the kidney is well known and prompts early investigation of the kidneys. Carcinomas of the kidney, even though clinically silent, are therefore often detected when the distant metastasis in the lung is the presenting sign.[3]

It is not to be implied that unduly prolonged periods of observations or investigations are recommended in order to exclude the possibility of metastatic tumor arising from a clinically silent extrathoracic primary tumor. It has been frequently demonstrated that routine investigations of systems and organs in the absence of symptoms or signs give low returns. The safety of thoracotomy recommends it as a therapeutic and diagnostic procedure. Should this not be feasible, radiation therapy should be carried out as a palliative alternative, although admittedly of uncertain benefit.

Radiation therapy was carried out in the six reported cases with G.E. 1000 KV HVL 3.7 Pb. 3 MA at 70 cm. distance. The treatment plan

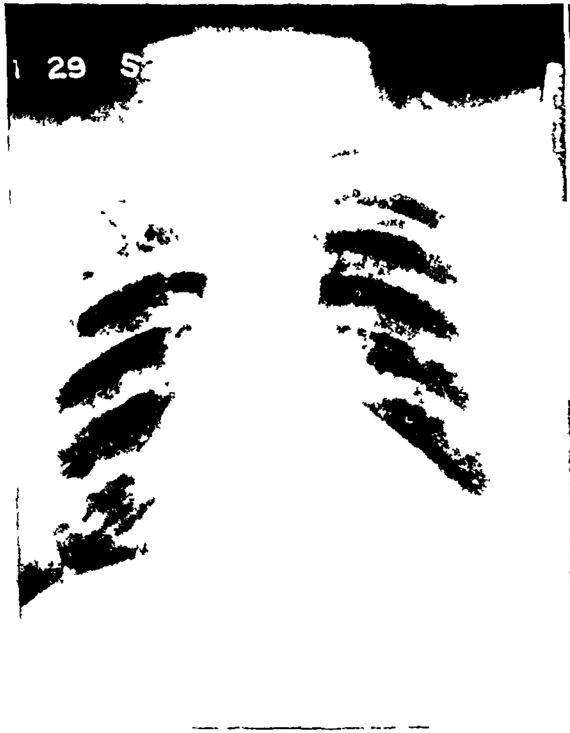

FIGURE 9

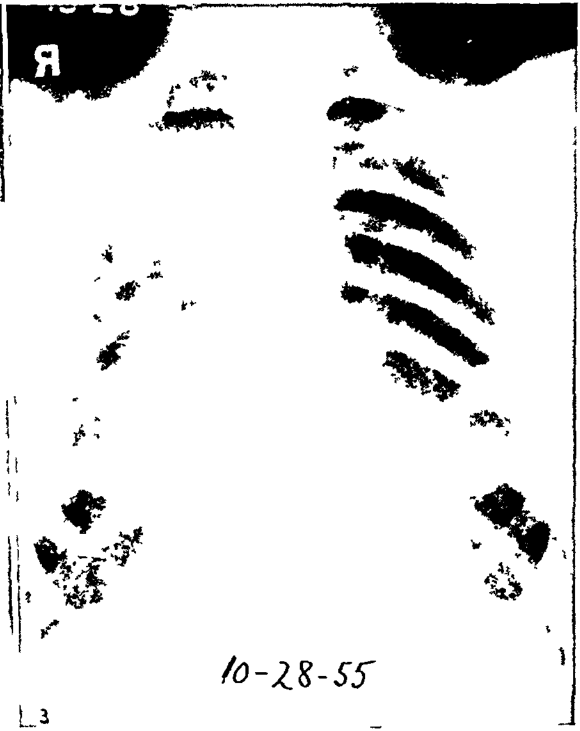

FIGURE 10

FIGURE 11

Figure 9 (Case 5): Primary tumor in prostate. Asymptomatic right upper lung solitary nodule.—*Figure 10* (Case 6): Primary tumor in kidney. Multiple cysts in right lung with fluid levels. Appearance on admission.—*Figure 11* (Case 6): Nodular densities in right upper lobe with fluid level in apex. Prior to right upper lobectomy.

consisted of the use of multiple converging fields aiming to deliver the equivalent of 6500r to the tumor in 30 days, as is our practice for bronchogenic carcinoma. Only in Case 4 was the dose substantially below this level. In Case 2 radiation caused complete regression of the lung masses and the patient survived a year from beginning of radiation. In the other five cases radiation therapy was of little or no benefit.

SUMMARY

Six cases of metastatic lung disease from occult primary sites, later proved to be in the pancreas, prostate and kidney, have been presented with the clinical, radiological and pathological features indistinguishable from bronchogenic carcinoma. Early diagnosis of such cases may not be possible.

Surgical exploration, if feasible, is the treatment of choice in pulmonary masses. Radiation therapy for palliation is recommended if malignancy is established or clinically diagnosed and surgery contra-indicated.

Extensive and prolonged diagnostic studies in order to prove the existence of a silent primary site is not in the patient's interest. Examination of the commonly reported sites, such as the genito-urinary and gastrointestinal tracts, could be carried out in a short period of time although frequently they fail to reveal the pathology.

RESUME

L'auteur présente six cas de cancer métastatique du poumon dont le foyer primitif n'a pu être mis en évidence et a été montré ultérieurement localisé au pancréas, à la prostate et au rein. Ces localisations pulmonaires avaient des caractères cliniques, radiologiques et pathologiques impossibles à différencier de ceux du cancer bronchique primitif. Le diagnostic précoce de tels cas peut ne pas être possible.

L'exploration chirurgicale, si elle est réalisable, est le traitement de choix des tumeurs pulmonaires. La radiothérapie, comme traitement palliatif, est recommandée si l'existence du cancer est établie ou soupçonnée cliniquement, et si la chirurgie est contre-indiquée.

Des études diagnostiques complètes et prolongées pour essayer de mettre en évidence l'existence d'une localisation primitive latente ne sont pas dans l'intérêt du malade. L'examen des localisations les plus habituelles, telles que celles des systèmes génito-urinaires et gastrointestinaux, pourrait être pratiqué en un court laps de temps, bien que fréquemment les examens anatomo-pathologiques ne peuvent être réal isés.

RESUMEN

Se presentan seis casos de metástasis pulmonares a partir de *primarios* ocultos que después se aclaró radicaban en páncreas, próstata y riñones, con las características clínicas, radiológicas y patológicas indistinguibles del carcinoma bronquiogénico.

El diagnóstico temprano de tales casos puede no ser posible. Si es factible, la exploración quirúrgica es el tratamiento de elección en las

masas pulmonares. Se recomienda la radioterapia paliativa si aclara la malignidad y la cirugía está contraindicada.

Los estudios extensos y prolongados para demostrar laexistencia de un tumor primario silencioso no corresponde al interés del enfermo.

El examen de los lugares más habitualmente afectados como las vías genitourinarias, la gastrintestinal, pueden realizarse en corto tiempo si bien frecuentemente no revelan la patología.

ZUSAMMENFASSUNG

Vorweisung von 6 Fällen von metastatischer Lungenerkrankung bei verborgenem Primärherd, der sich später als im Pankreas, in der Prostata und Niere lokalisiert erwies, und zwar anhand der klinischen, röntgenologischen und pathologisch-anatomischen Merkmale nicht zu unterscheiden vom Bronchialcacinom. Die Früh-Diagnose solcher Fälle kann unmöglich sein.

Untersuchung auf chirurgischem Wege, falls sie sich durchführen lässt, ist die Behandlung der Wahl bei pulmonalen Verdichtungen. Palliative Strahlenbehandlung wird empfohlen, wenn die Bösartigkeit sicher gestellt oder klinisch diagnostiziert und chirurgisches Vorgehen kontraindiziert ist. Intensive und langdauernde diagnostische Untersuchungen mit dem Ziel, das Bestehen, eines stummen Primärherdes nachzuweisen, liegt nicht im Interesse des Kranken. Untersuchung der für gewöhnlich angegebenen Lokalisation, also des Urogenitaltraktes und des Magen-Darmkanales lassen sich in kurzer Zeit ausführen, obwohl sie häufig darin versagen, die krankhaften Umstände aufzudecken.

REFERENCES

1 Abeles, H. and Ehrlich, D.: "Single Circumscribed Intrathoracic Densities," *New England J. Med.*, 244:85, 1951.

2 Acherman, L. V. and del Regato, J. A.: Cancer. St. Louis, 1954, C. V. Mosby Co. (2nd Edition).

3 Beer, E.: "Some Aspects of Malignant Tumors of the Kidney," *Surg., Gynec. and Obst.*, 65:433, 1937.

4 Brezina, P. S. and Lindskog, G. E.: "Total Pneumonectomy for Metastatic Uterine Carcinoma," *J. Thoracic Surg.*, 12:728, 1943.

5 Churchill, E. D.: "Primary Carcinoma of the Lung," *J.A.M.A.*, 137:455, 1948.

6 Clerf, L. H.: "Melanoma of Bronchus; Metastasis Simulating Bronchogenic Neoplasm," *Ann. Otol., Rhin. and Laryng.*, 43:887, 1934.

7 Condon, W. B.: "Round Lesion of the Lung in Older Persons," *in Thoracic Surgery Seminar*, Denver, Fitzsimons Army Hospital, 1952, pp. 23-26.

8 Effler, D. B.: "Solitary Lung Tumors," *Am. Rev. Tuberc.*, 63:252, 1951.

9 Effler, D. A., Blades, B. and Marks, E.: "The Problem of the Solitary Lung Tumors," *Surgery*, 24:917, 1948.

10 Elkin, M. and Mueller, H. P.: "Metastases from Cancer of the Prostate; Autopsy and Roentgenological Findings," *Cancer*, 7:1246, 1954.

11 Ewarts, E. E.: "Apparently Unilateral Solitary Pulmonary Metastasis from Renal Cell Carcinomas," *Surg. Clinics of N. A.*, 34:801, 1954

12 Farrell, J. T.: "Pulmonary Metastasis; a Pathologic, Clinical Roentgenologic Study Based on 78 Cases Seen at Necropsy," *Radiology*, 24:444, 1935.

13 Foggie, W. E. and Turhope, G. R.: "Secondary Carcinoma of Lung with Inconspicuous Primary in the Gallbladder," *Edinburgh Med. J.*, 37:632, 1930.

14 Freelander, S. O. and Greenfield, J.: "Hemoptysis in Metastatic Tumors of the Lung Simulating Bronchogenic Carcinoma," *J. Thoracic Surg.*, 12:109, 1942.

15 Fried, J. R.: "Skeletal and Pulmonary Metastases from Cancer of the Kidney, Prostate and Bladder," *Am. J. Roentgenol. and Rad. Therapy*, 55:153, 1946.

16 Graves, R. C. and Militzer, R. E.: "Carcinoma of Prostate with Metastasis," *J. Urology*, 33:235, 1935.

17 Grow, J. B., Bradford, M. L. and Mahon, H. W.: "Exploratory Thoracotomy in the Management of Intrathoracic Disease," *J. Thoracic Surg.*, 17:480, 1948.

18 Higginson, J. F.: "A Study of Excised Pulmonary Metastatic Malignancies," *Am. J. Surg.*, 90:241, 1955.

19 Hodgson, C. H. and McDonald, J. R.: "The Diagnosis and Management of Solitary Circumscribed Lesions of the Lungs," *Dis. Chest*, 24:289, 1953.

20 Hood, R. T., McBurney, R. P. and Clagett, O. T.: "Metastatic Malignant Lesions of the Lungs Treated by Pulmonary Resection; A Report of 43 Cases," *J. Thoracic* Surg., 30:81, 1955.

21 King, D. C. and Castleman, B.: "Bronchial Involvement in Metastatic Pulmonary Malignancy," *J. Thoracic Surg.*, 12:305, 1943.

22 Kirklin, J. W., McDonald, J. R., Glagett, O. T., Moersch, H. J. and Gage, R. P.: "Bronchogenic Carcinoma; Cell Type and Other Factors Relating to Prognosis," *Surg., Gynec. and Obst.*, 100:429, 1955.

23 Mandeville, F. B.: "Roentgen and Clinical Problems in So-Called Solitary Metastatic Tumors in the Chest," *Am. J. Surg.*, 71:669, 1946.

24 Meckstroth, C. V., Andrews, N. C. and Klassen, K. P.: "Surgery for Solitary Lesions of the Lung," *A.M.A. Arch. Surg.*, 69:220, 1954.

25 Raine, F.: "Metastatic Carcinoma of the Lung Invading and Obstructing a Bronchus," *J. Thoracic Surg.*, 11:216, 1941.

26 Russo, P. E. and Cavanaugh, C. J.: "Diagnosis of Pulmonary Metastases: A Study of 105 Cases," *Radiology*, 60:198, 1953.

27 Springer, D. W., Geiger, P. E. and Langston, H. T.: "Rounded Intrathoracic Lesions," *Am. J. Roentgen.*, 74:827, 1955.

28 Tinney, W. S. and McDonald, J. R.: "Pulmonary Metastasis of Carcinoma Diagnosed by Bronchoscopy," *Minnesota Medicine*, 28:554, 1945.

29 Turner, J. W. and Jaffe, H. L.: "Metastatic Neoplasms; A Clinical and Roentgenological Study of Involvement of Skeleton and Lungs," *Am. J. Roentgenol. and Rad. Therapy*, 43:479, 1940.

30 Vinson, P. P. and Martin, W. J.: "Pulmonary Metastasis from Hypernephroma Diagnosed by Bronchoscopy," *Arch. Otolaryn.*, 15:368, 1932.

31 Weiss, E.: "The Differential Diagnosis of Primary and Secondary Carcinoma of the Bronchi," *Am. J. Med. Sc.*, 177:487, 1929.

32 Wilkins, E. W.: "The Asymptomatic Isolated Pulmonary Nodule," *New England J. Med.*, 252:515, 1955.

33 Willis, R. A.: *Spread of Tumors in the Human Body*,. C. V. Mosby Co., St. Louis, 1952.

34 Wolpaw, S. E.: "The Diagnosis and Management of Asymptomatic Isolated Intrathoracic Nodules," *Ann. Int. Med.*, 37:489, 1952.

Study in the Therapy of Transverse Myelitis Occurring During Tuberculous Meningitis

P. CHORTIS, M.D., F.C.C.P.
Athens, Greece

Transverse myelitis appearing during the course of tuberculous meningitis is one of the main reasons for its poor prognosis. Fortunately, this condition is relatively infrequent and, it is possible with prompt and appropriate therapy it can be significantly reduced.

Spreading of the infection in the medulla spinalis is mainly due to contamination of the meninges during tuberculous meningitis. Localization of Mycobacterium tuberculosis in the medullar substance through the circulation in generalized tuberculosis is uncommon.

In the international literature, only a few cases of tuberculous meningomyelitis are reported. Kupka and his collaborator, Harbitz, Kreschner and his collaborator, and Rigton, have presented a number of cases.

Fischer reported 20 cases of myelitis in the course of tuberculous spondylitis caused by compression of vertebrae and cold abscess formation.

At Sotiria Sanatorium, in our clinic, we treated 209 cases of tuberculous meningitis and observed only six cases of transverse myelitis, which appeared in the course of tuberculous meningitis insufficiently treated at places other than our institution. Three of them died, and necropsies were performed.*

Report of Cases

We consider essential the detailed presentation of cases in order to render our conclusions clearer.

Case 1: D. M., a man clerk, aged 27, was found to have pulmonary tuberculosis in August 1952. Biochemical treatment for eight months was insufficient. In 1952, he had tuberculous meningitis and for 55 days he was treated insufficiently in his house. Treatment there consisted of intraspinal injections of streptomycin combined with small doses of INH. In March 1953, he was transferred to our clinic. He had a high fever, dimness of mental functions, spasms with hyperexcitability and all the clinical symptoms of meningitis. Laboratory examination of cerebrospinal fluid showed 650 cells per cc., 96 per cent being lymphocytes and 2.5 gr./100 cc. of protein and Mycobacterium tuberculosis.

Other findings were rectovesical disturbances, spastic paresis of the lower extremities with heightened tendon reflexes, disturbance of sensitivity and extensive necrotic changes of the gluteal and sacrolumbar skin regions. Thus, it was as a meningomyelitis case.

Intraspinal streptomycin was discontinued and followed by persistent antituberculous drug therapy. Improvement of meningitis was marked. The cerebrospinal cell count fluid and protein decreased. The medullar symptoms, however, were accentuated, the spastic paresis turned flaccid, the retentions of urine and feces increased, as well as the skin necroses. The patient's condition progressively became worse and four months later he died.

On post-mortem examination the brain was edematous, the cerebral ventricles dilated and filled with turbid cerebrospinal fluid; in the base of the brain a considerable amount of viscous and glutinous exudate was found; the spinal meninges were much thickened and in places, small pockets of fluid adhered; in the thoracic region of the spinal column, a good sized pocket of fluid was found where the pia mater firmly

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Director, 8th Clinic Hospital Sanatorium Sotiria.

*The histology examinations were made by Professor D. Eleftheriou to whom we extend our thanks.

adhered to the spinal cord. Transverse dissection at this very point showed complete transverse degeneration with necroses, and it was impossible to distinguish between the white and grey matter. Histological study revealed, in addition to necrotic and degenerative substances which occupied all the transverse segment of the cord, peripheral necrosis like a geographical map. In the destructive changes of medullar substance, scattered tubercles were found. The walls of the vessels of the subarachnoid cavity were infiltrated and many of them were completely plugged. The vessels of the spinal meninges showed periadventitial infiltrations with many tubercles.

We concluded that it was a case of diffuse transverse myelitis involving the thoracic region of the spinal cord, caused by bacilli localization in the medullar substance from contiguous tissues. In this case, the accentuation of the disease and the diffuse destruction of the transverse medullar segment was due to the progressive compression of the spinal cord by the encysted pocket of fluid. This pocket formation was due to the adherent meninges.

Case 2: S. D. This man, a laborer aged 32, reported having pulmonary tuberculosis in March 1952. In March 1953, he had tuberculous meningitis and was hospitalized. For three months, the treatment consisted of intraspinal injections of streptomycin and small doses of INH. In June 1953, he was transferred to our clinic, when he had fever, opisthotonos, and total mental dimness. Cerebrospinal fluid examination showed 770 cells per cc. and 16 gr./100 cc. of protein. Spastic paresis of the lower extremities, positive Babinski plantar reflex, foot clonus, exaggerated reflexes, and hyperthesia were also present. Other findings were rectovesical disturbances, e.g., alternate retention and loss of rectal and vesical control.

Although the intraspinal injections of streptomycin were discontinued and large doses of INH and PAS were intravenously administered, he became worse. A month and a half later, spastic paresis turned flaccid, extensive nutritional disorders of the skin appeared, and loss of rectal and vesical control occurred. His condition gradually became worse, and in the fourth month following hospitalization he died.

Post-mortem findings revealed marked increase of cerebrospinal fluid with edematous encephalic substance. The spinal meninges were thickened and at places adherent to themselves and the medulla spinalis. In certain points between the meninges small pockets of turbid fluid were found; dissection at the adherent points of the medullar substance and the pia mater showed degenerative changes and necroses of the whole transverse segment; the histological findings showed degenerative necrotic destruction of the medullar substance with small, sparse tubercles; infiltrations and thromboses of the vessels of the subarachnoid cavity and extensive degenerative changes of the spinal meninges were also found. We concluded that this was a case of diffuse transverse myelitis with multiple foci in the medullar substance.

Case 3: I. D., male. This farmer, aged 45, had pulmonary tuberculosis five years ago. In April 1953, he had tuberculous meningitis and entered a hospital. Treatment consisted of intraspinal injections of streptomycin, PAS, and INH. The second month following the intraspinal injection therapy, although he showed slight clinical improvement, medullar phenomena appeared. He was admitted to our clinic. His condition was grave. Besides meningitis symptoms and the findings in the cerebrospinal fluid, he also had flaccid paralysis of the lower extremities, loss of rectal and vesical control, and extensive skin necroses.

Intraspinal injections were discontinued and usual chemotherapy followed. His condition, however, progressively became worse and in two months, that is five months following the infection, he died. Microscopic study revealed multiple diffuse transverse spinal destruction in different levels. Small tubercles in the medular substance were also seen. Extensive adherent processes of the spinal meninges, accompanied by periadventitial infiltrations and a plugging of the vessels, were also seen. We concluded that it was a tuberculous meningomeylitis case with multiple medullar foci.

Case 4: P. E. This laborer aged 21 had acute miliary tuberculosis in March 1952. Two years later, tuberculous meningitis was present. He was treated insufficiently with intraspinal injections of streptomycin, PAS, and INH. After two months of therapy, he also had symptoms of meningomyelitis.

He was transferred to our clinic with meningitis symptoms; abundant cerebrospinal fluid findings, spastic paresis of the lower extremities, exaggerated reflexes, positive Babinski's sign, foot clonus, nutritional skin disorders and rectovesical disorders.

Intraspinal injections were immediately discontinued and usual chemotherapy was initiated, supplemented by 12 mgs. per Kg. body weight of Sulfone J.51, daily.

Ten days later his condtion improved considerably and within 45 days, all meningitis symptoms had disappeared. Medullar symptoms were also improving. Four and a half months later, almost all spinal symptoms had disappeared to the point that he could move freely. A slight spastic gait was the sole effect of the disease, which with electrotherapy and massage was improved to the extent that he was discharged as clinically cured. A year later, he was in excellent condition, exhibiting only a slight spastic gait.

We conclude in this case that the J. 51 addition in meningomyelitis treatment contributed to the cure of the disease, leaving few residuals.

Case 5: S. I. This man a clerk aged 26, was hospitalized for tuberculous meningitis in February 1952. He was treated insufficiently with intraspinal injections of streptomycin and INH. In May 1954, he had a new paroxysm of meningitis and was brought to our clinic. He also had transverse myelitis symptoms affecting the lumbar region of the spinal cord. The cessation of intraspinal injections was followed by intravenous administration of INH, PAS, and sulfone J.51, 14 mg. per Kg. body weight. After four months of treatment the meningitis symptoms disappeared altogether, the cerebrospinal fluid was normal, and the myelitis symptoms showed improvement. The rectovesical and nutritional disorders of the skin disappeared. Sensitivity became normal, and the spastic paresis of the extremities improved.

Eight months after this therapy was started, he was clinically cured except for a slight spastic walk, which was treated with electrotherapy, massage, and vitamin B, besides the other medication. He was dismissed in excellent condition.

Case 6: G. L. This man a student aged 22, had exudative pleurisy in March 1955. Eight months later, he was treated for tuberculous meningitis in a State hospital. The three-month treatment consisted of intraspinal injections of streptomycin and small amounts of PAS and INH with no evident improvement. Moreover, he had rectovesical disorders and spastic paresis of the extremities. When admitted to our clinic he had chronic tuberculous meningitis and transverse myelitis. Discontinuation of intraspinal injections was followed by large doses of INH, PAS, and sulfone J.51 in doses of 14 mg. per Kg. body weight. This treatment was continued for six months. The meningitis symptoms disappeared, the cerebrospinal fluid became normal and urine and feces retentions as well as skin abnormalities disappeared. The spastic paresis of the extremities improved. After eight months, he was dismissed as chronically cured with only a slight spastic walk residual.

Comment

Myelitis, depending on the total or partial damage of the transverse segment of the cord, is distinguished as diffuse or disseminated respectively. According to its duration, it is designated as acute, subacute, or chronic. Symptomatology depends upon type and extent of damage to the medullar substance. In acute myelitis symptoms appear at once and consist of total disappearance of mobility, anesthesia, as well as loss of reflexes caudal to the damage, consequent of which is flaccid paralysis of the lower extremities, vesica urinaria, and rectum, and extensive nutritional disturbances of the skin in the form of necroses also appear. On the other hand, the symptomatology of subacute or chronic myelitis is different and appears gradually. The reflexes do not disappear, muscle tone remains, rectovesical disorders alternately improve or grow worse. The nutritional disturbances of the integument appear gradually and are localized, Babinski's sign and foot conus appear early, and areas inferior to the damage have normal sensation.

The first three of our cases were diffuse transverse myelitis, as destruction involved the whole segment of the cord. In the last three subacute disseminated cases, the lesions, because of the intense therapeutic administration and especially because of the addition of sulfone J.51, not only did not extend but were even inhibited and gradually healed, leaving slight after effects in the motor region of the cord.

Through detailed tests of the reaction and sensitivity of the skin from the inferior towards the superior layer, we found that in the first case of transverse myelitis the thoracic region of the column was affected. In the second and third cases the myelitis was located in the thoracolumbar and sacral regions respectively. Morbid anatomy verified our findings. In the remaining three cases, we proved clinically that the damage was in the lumbar region and that the destruction was disseminated. Necropsy also revealed that the destruction in the first three cases was diffuse. In the first case, in addition to necrotic and degenerative changes of the white and grey substance, sparse tubercles were also found. The walls of the vessels of the subarachnoid cavity were infiltrated and plugged. At the points where there were destructive changes in the medulla the pia mater was firmly adherent to the medulla spinalis. Between the two meninges there was a pocket of turbid fluid, the walls being the adhesions of the two meninges.

From the above, one may conclude that the infection of the medullar substance was caused by direct extension, and the peripheral necroses were due to a plugging of the vessels. The total damage of the transverse segment was caused not only because of the tuberculous localization but mainly from the gradual compression of the medullar segment by the encysted pocket of fluid.

In the second and third cases, besides total transverse destruction in different levels of the cord, we also found a complete adherent process of the meninges, as well as multiple tiny pockets of turbid cerebrospinal fluid, in the whole of the vertebral canal.

It is known that such localized or extended medullar necroses are also caused by cancer, syphilis, and arteriosclerosis. The differential diagnosis, however, is based on laboratory, clinical and x-ray findings.

In the remaining three cases, the cessation of intraspinal injections was followed by persistent biochemical therapy with large intravenous doses of INH and PAS and, in addition, doses of 12-14 mg. per Kg. body weight of sulfone J.51. As a result, the subacute disseminated transverse myelitis showed no tendency to grow worse, but on the contrary the symptoms gradually disappeared and the patients were finally discharged as clinically cured with only slight effects from the motor region of the spinal cord. For over a year, the patients are seen regularly and their condition is excellent.

In all our cases of tuberculous meningomyelitis, prolonged therapy of intraspinal injections of streptomycin had preceded. We believe that this point is of considerable importance.

As was reported in a previous study that streptomycin injected intraspinally causes intensive stimulation of the meninges. This is proved by the fact that following intraspinal injections a considerable increase of cells in the spinal fluid is noted, accompanied by paroxysms with meningeal symptoms. In certain cases during intraspinal administration of streptomycin and during the period of improvement, we observed that the disease grew worse. We interpreted this as recurrence. However, the paroxysms disappeared as soon as the intraspinal injections of streptomycin were discontinued. The intensive stimulation of the meninges by streptomycin and the daily injury from the needle contributed to the formation of adherent processes and their disagreeable consequences. In all of the dissected cases in which intraspinal injections had been given, extensive adhesions of the meninges with encysted pocket formations filled with cerebrospinal fluid with corresponding medullary destruction was a constant finding. The paroxysm of the meninges, inflammation, and the adhesion process contribute to the expansion of contamination in the medullary substance and the destruction of the vessels of the subarachnoid cavity, resulting in deficient blood supply to the medullar substance and consequently a degeneration and necroses of the corresponding medullar segments.

Having this in mind, we have for some years omitted intraspinal injections of streptomycin, and since then, have never observed a case of meningomyelitis.

Special attention should be drawn to the fact that in three out of six cases in which, in addition to antituberculosis drugs, we also administered J.51, we succeeded in preventing further meningomyelitis developments and in bringing about an almost complete cure. We have used J.51 (Sulfone thymole) for three years in our clinic at Sotiria Sanatorium.[6, 7] The results were excellent, especially in the treatment of tuberculous meningitis, since 96.7 per cent of the patients recovered completely. They are still immune after long treatment and by treatment in large dosages. The effectiveness and immunization is confirmed by other authors. Furthermore, the advantage of J.51 is that it retards the occurrence of streptomycin resistance.

We cannot yet give an explanation for the way J.51 acts in the treatment of tuberculous meningitis and myelitis. All our attempts to trace the drug in the cerebrospinal fluid, blood, and urine have failed. A good number of investigators feel that J.51 *in vivo* breaks up and great amounts of it diffuse in pathologic tissue where it stays for a long time coming in constant contact with the pathologic agent. The foregoing conception, however, does not have a laboratory basis. Undoubtedly, however, J.51 has a valuable therapeutic effect in tuberculous meningitis and myelitis.

CONCLUSIONS

1. In a considerable number of cases of tuberculous meningitis, transverse myelitis may occur and localization of bacilli in the medulla spinalis is primarily due to direct extension.
2. Myelitis appears in cases of prolonged and incomplete therapy of tuberculous meningitis and mainly when intraspinal injections of streptomycin have been administered for a long time.
3. Sulfone J.51 has a considerable therapeutic effect on meningomyelitis, and especially when administered before complete degeneration and necrosis of a spinal segment.
4. Histologic changes of myelitis consist of degenerative and necrotic changes of white and grey matter, accompanied by development of tubercles as well as extensive changes in the subarachnoid cavity vessels.

CONCLUSIONES

1. En un número considerable de casos de meningitis tuberculosa puede ocurrir la mielitis transversa y localización de bacilos en la médula, se debe en primer lugar a retención.

2. La mielitis aparece en casos de terapéútica prolongada e incompleta de la meningitis tuberculosa y principalmente cuando se han hecho inyecciones intraespinales de estreptomicina por largo tiempo.

3. La sulfona J.51 tiene un efecto terapéutico considerable en la meningomielitis y especialmente cuando se administraantes de la degenearación y necrosis de un segmento espinal.

4. Los cambios histológicos de la mielitis consisten en degeneración y necrosis de las substancias blanca y gris acompañadas de desarrollo de tubérculos así como extensos cambios en los vasos del espacio subaracnoideo.

RESUME

1. Dans un grand nombre de cas de méningite tuberculeuse, une myélite transverse peut survenir, et la localisation des bacilles dans la moelle épinière est due en premier lieu à la rétention directe.

2. La myélite apparait dans les cas de traitement prolongé et incomplet de méningite tuberculeuse, et principalement lorsque injections intrarachidiennes de streptomycine ont été administrées pendant longtemps.

3. La sulfone J.51 a un effet thérapeutique considérable sur la méningomyélite, et surtout lorsqu'elle est administrée avant la dégénérescence complète et la nécrose d'un segment médullaire.

4. Les altérations histologiques de myélite consistent en altérations dégénératives et nécrotiques de la matière grise et de la matière blanche, associées à l'apparition de tubercules ainsi que d'altérations extensives dans des vaisseaux de la cavité sous-arachnoïdienne.

SCHLUSSFOLGERUNGEN

1. In einer beträchtlichen Zahl von Fällen von tuberkulöse Meningitis kanne eine Querschnitts-Myelitis auftreten, und die Lokalisation von Bazillen in der medulla spinalis ist in erster Linie die Folge dirkterRetention.

2. Die Myelitis tritt auf in Fällen von langdauernder und unvollständiger Therapie der tuberkulösen Meningitis und hauptsächlich, Wenn von intralumbalen Streptomycin-Injektionen lange Zeit hindurch Gebrauch gemach wurde.

3. Die Schwefelverbundung J51 übt einen beträchtlichen therapeutischen Effekt aus auf die Meningomyelitis, besonders bei Anwendung von kompletter Degeneration und Nekrose eines spialen Segmentes.

4. Die histologischen Veränderungen der Myelitis bestehen in degenerativen und nekrotischen Veränderungen der weissen unr grauen Substanz in Verbindung sowohl von Tuberkeln als auch ausgedehnten Veränderungen an den Gefässen des Subarachnoidalraumes.

BIBLIOGRAPHY

Basset, A.: "Peut-on prejuger du mode d'action des sulfones dans la lepre. Notre experience actuelle." *La Semaine des Hopitaux de Paris.* 32:3, 1956.

Cafiero, F., Cogo, L., Gemelli, D. et Scialpi, G. L.: "Contributo alla terapiea della tuberculosi polmonare con un Solfone timolato argentico," *Giornale Italiano della Tuberculosi,* 10:3, 1956.

Chortis, P.: "La contribution de la sulfone thymolée au traitement de la tuberculose," *Le Poumon et le Coeur* (Paris), 6:487 1955.

Chortis, P.: "Le traitement actuel de la méningite tuberculeuse," *Le Poumon et le Coeur* (Paris), 5:475, 1956.

Chortis, P.: "Results of the Treatment of Tuberculosis Meningitis," Communication 4. Congres International des Malades du Thorax de l'American College of the Chest Physicians, Cologne, Germany, August 1956, Page 502.

Cotereau, H. Y., Marquiset, J. P., et al.: Premieres recherches biochimiques sur une sulfone thymolee. Comptes rendus des seances de la Societe de Biologie Paris. Seance June 11, 1955. 149:1142, 1955.

Cotereau, H. Y., Marquiset, J. P. et al.: Nouvelels recherches sur la sulfone bisazoique thymolee. Comptes rendus des seances de la Societe de Biologie Paris. Seance November 26, 1955. 194:1950, 1955.

Escolivat, J.: Chef due Service de Sante (Territoire des Comores-Madagascar). Rapport officiel. December 21, 1955.

Gouvernement General de la A.O.F., Institut Marchoux, Service de la lepre. Rapport officiel. December 23, 1955.

Grenier, J., Bavay, J. et al.: "Essais de prevention des adherences meningees dans les pie-merites tbc. par la sulfone diargentique." *La Presse Medicale.* 62:1406, 1954. *ABSTRACT*: in J.A.M.A., 157:393, 1955.

Institut Pasteur de Saigon (Sud Vietnam): Traitement de la lepre par le Sulfone J. 51. Rapport annuel de Laboratoire de Microbiologie humaine de l'Institut Pasteur, 1954.

Kahan-Lemaire, G.: "Essai de prévention des adhérences dans le meningities tbc. par la sulfone argentique." Thése Doct Med., Paris, Mars, 1954 (Vigot Fréres) Edit.

Rist, N., Boyer, F., Saviard, M. et Hamon, V.: "Sur le mode d'action d'une sulfone thymolée argentique," *Rev. de la Tbc.*, 18:179, 1954 (Paris).

Legger, H.: "Le traitement medical prolonge des tuberculoses pulmonaires anciennes," *Les nouvelles therapeutiques*, 7:9, 1956.

Leproserie de Mantivu, Ceylon. Rapport officiel, 1956.

Morales and Romero-Giron, M.: "Tratamiento de la tuberculosis pulmonar con la sulfona J. 51," *Rev. Esp. de Tbc.*, 24:67, 1955.

Mystakas, G. and Michalopoulos, A.: "Observations de diabete sucre et nephrose sur terrain tuberculeux traitees par le Sulfonatox," *Acta Tuberculosa Graeca*, 17:50, 1956.

Peco-Lapoulide, F.: La Sulfona J.51 en la diabetes. Communicacion al Congresso Internacional de la Tuberculosis. October 1954. (Madrid, Spain.)

Navarro Gutierez, R., Soria, A.: "Resultados del estudio clinico de la aplicacion de la sulfona J.51 (Timosulfon) en el tratamiento della tbc. pulmonar y osteoarticular," *Rev. Esp. de Tuberc.*, 24:569, 1955.

Rigton, R. H.: "Transverse Myelitis Accompanying Tub. Meningitis," *Am. Rev. Tuberc.*, 55:332, 1947.

Roy, A. T.: D.M.51. Antiseptic, Sept. 1955. Abstract: in *J.A.M.A.*, 160:75, 1956.

Tysebaert, J.: "Notes a l'egard d'utilization de la Sulfone J. 51 dans le traitement de la tuberculeuse pulmonaire," *Le Scalpel*, 107:771, 1954.

Tzanck, A., Basset, A. and Salomon, L.: "Nouvelles observations sur le traitement prolonge de la lepre at de la tbc." *Bulletins et Memoires de la Societe Medicale des Hopitaux de Paris*, 69:715, 1953. Abstract: in *J.A.M.A.*, 154:163, 1954.

Tzanck, A., Basset, A., Salomon, L.: "Action prolongee d'un nouvel antibiotique atoxique dans le traitement de la lepre," *La Presse Medicale*, 61:249, 1953. Abstract: in *J.A.M.A.*, 152:978, 1953.

Urquia, D. A.: "Proprietes bacteriostatique d'une sulfone thymole," *Comptes rendus des seances de la Societe Biologie*," 149:1948, 1955.

Vaisseau, M. Col., Silverie, M. Comm.: Resultats d'une experimentation sur des lepreux traites par la sulfone J. 51 au Cameroun (Leproserie de la Dibamba). Gazette Medicale de France. 63: April 10, 1956.

Weiller, P.: "L'action retardante de la sulfone thymolée argentique sur l'apparition de la streptomycino-resistance," *Revue de la Tbc.*, 20:349, 1956 (Paris).

Weiller, P.: "La sulfone argentique dans le traitement de la pulmonaire," *Les Nouvelles Thérapeutiques*, 5:7, 1954 (Paris).

Weiller, P. and Rymer, M.: "A propos d'une nouvelle sulfone et de son interet dans le traitement de la tuberculose pulmonaire," *Le Poumon et le Coeur*, 8:747, 1952.

Weiller, P.: "La sulfone J.51 dans le traitement de la tuberculose pulmonaire," *Les Nouvelles Therapeutiques*, 5:7, 1954.

Weiller, P. and Legger, H.: "Le traitement des fistules tbc. ganglionnaires et osseuses par la sulfone J. 51," *Le Poumon et le Coeur*, 10:199, 1954.

SECTION ON CARDIOVASCULAR DISEASES

Differentiation of the Causes of Pulmonary Hypertension in Rheumatic Heart Disease by Simultaneous Right and Left Heart Catheterization[*,**]

PHILIP SAMET, M.D., F.C.C.P.,[1] WILLIAM H. BERNSTEIN, M.D.
and ROBERT S. LITWAK, M.D.[2]
(*With the collaboration of H. Turkewitz, M.D., Leonard Silverman, M.D.
and Milton Lesser, M.D.*)
Miami Beach, Florida

Pulmonary hypertension in patients with rheumatic heart disease is induced by pulmonary vascular disease, mitral valve block, left heart failure or any combination of these entities.[1,2] Exact differentiation between these various possibilities is difficult on clinical grounds or with the aid of right heart catheterization. The purpose of this report is to demonstrate how combined and left heart catheterization can facilitate solution of this problem and shed light on the clinical and physiologic abnormalities in mitral and/or aortic valve disease.

Methods

Right heart catheterization and arterial cannulation are performed via the same arm in the usual manner in the basal post-absorptive state to permit determination of the cardiac output by the Fick principle. Multiple steady rate pressure and cardiac output determinations are made at rest, and during exercise and recovery. Whenever possible, double-lumen or triple-lumen catheters are used to permit simultaneous pressure recording from multiple sites in the right heart and pulmonary artery. With the right heart catheter and brachial artery needle in situ, the patient is turned to the prone position. Repeat right heart pressures are obtained. Meperidine Hydrochoride (50-75 mg.) is given intramuscularly at this point.

Left heart catheterization is performed by a modification of the posterior percutaneous puncture technique of Fisher.[3] Fluoroscopic visualization of the left atrium is performed in the prone position. Two six or seven

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[*] From the Cardio-Pulmonary Laboratory and the Department of Medicine, Mt. Sinai Hospital, Miami Beach, Florida, and the Division of Cardiology of the Department of Medicine and the Department of Surgery, University of Miami School of Medicine, Coral Gables, Florida, and Jackson Memorial Hospital, Miami, Florida.

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[1] Director, Cardio-Pulmonary Laboratory, Mt. Sinai Hospital; Assistant Professor of Medicine, University of Miami School of Medicine.

[2] Assistant Professor of Surgery, University of Miami School of Medicine; Attending Surgical Staff, Jackson Memorial Hospital.

inch No. 17 thin-walled styletted needles are inserted into the left atrium. Polyethylene tubing is then passed through these needles into the left atrium and left ventricle. Simultaneous pressures are obtained (from the same baseline and at identical strain gauge sensitivities[4]) from the left atrium, left ventricle and brachial artery in the prone position.

Whenever possible, the left heart needles are removed at this point in a fashion such that the polyethylene catheters remain in the left atrium and left ventricle respectively. The patient is carefully returned to the supine position. These positional changes are facilitated by the prior insertion of the brachial artery needle and right heart catheter in the same arm thereby leaving the other upper extremity free to aid in the changes in position. After a suitable rest period to permit return to the steady state, repeat measurements of the right and left heart pressures and cardiac output are performed at rest and exercise.

All pressure measurements are made on a six channel photographic recorder* employing Statham strain gauges P23AA, P23D and more recently P23G. Blood gas analysis is performed by standard techniques on a Van Slyke manometric apparatus. Expired gas analyses are carried out with a Scholander gas analyzer.

In the supine position the reference level for right heart pressures is 5 cm. dorsal to the angle of Lewis. In the prone position the reference level is also 5 cm. dorsal to this angle. A level 10 cm. dorsal to the angle of Lewis has been adopted as the zero level for left heart pressure in this study in both supine and prone positions.

Materials

Fifty-five simultaneous combined right and left heart catheterizations have been performed to date in 45 patients; mitral valve disease was present in 33 of these patients. Eleven combined and two right heart catheterizations in five patients have been selected to illustrate the afore-mentioned causes of pulmonary hypertension in patients with rheumatic heart disease. D.D., a 40 year old white man was investigated pre-operatively, and one month and 10 months post-operatively with right and left heart catheterization. S.B., a 41 year old colored woman was catheterized before surgery and one and 12 months post-surgery, with right and left heart catheterization. J.V., a 32 year old white woman was studied before surgery and 11 months after surgery with combined heart catheterization, in addition to right heart studies one and two months after commissurotomy. R.R., a 30 year old white woman was catheterized before surgery and one month after commissurotomy with combined heart catheterization. The diagnosis in these four subjects before surgery was pure mitral stenosis. The fifth patient, S.M., a 48 year old white man, had severe aortic stenosis with minimal aortic insufficiency; simultaneous right and left heart catheterization was performed during the evaluation work-up. He refused surgical intervention and died one month later.

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*Electronics for Medicine, White Plains, N. Y.

Results

Pulmonary hypertension due predominately to mitral valve block is illustrated in Figures 1-5; these curves were obtained in R.R., a 30 year old white woman. Pulmonary hypertension is present at rest pre-operatively, with a further increase noted during exercise, (Fig. 1). Left heart catheterization revealed a large left atrial—left ventricular mean diastolic gradient, 16 mm. Hg at rest. On exercise the gradient rose to 24 mm. Hg. (Fig. 2). One month after surgery pulmonary artery pressure was

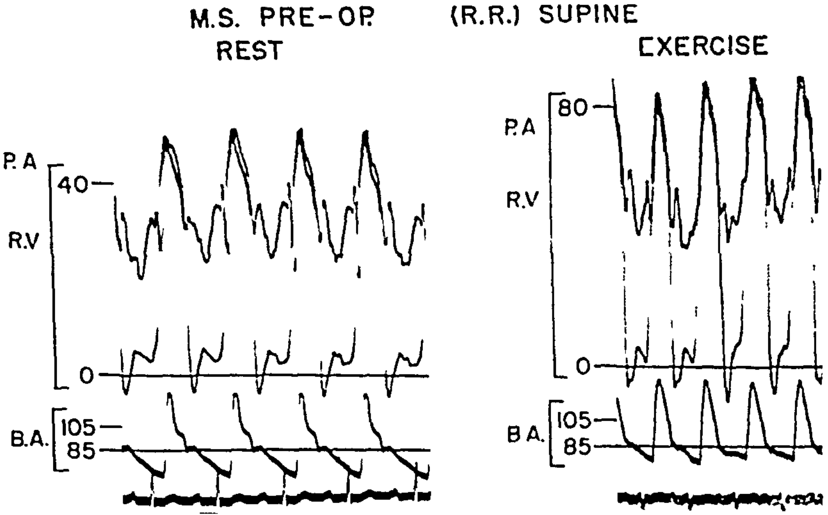


FIGURE 1: Pulmonary artery, right ventricle and brachial artery pressure curves in R. R. before surgery. The resting pulmonary hypertension is further increased during exercise. Paper speed 25 mm. per second.

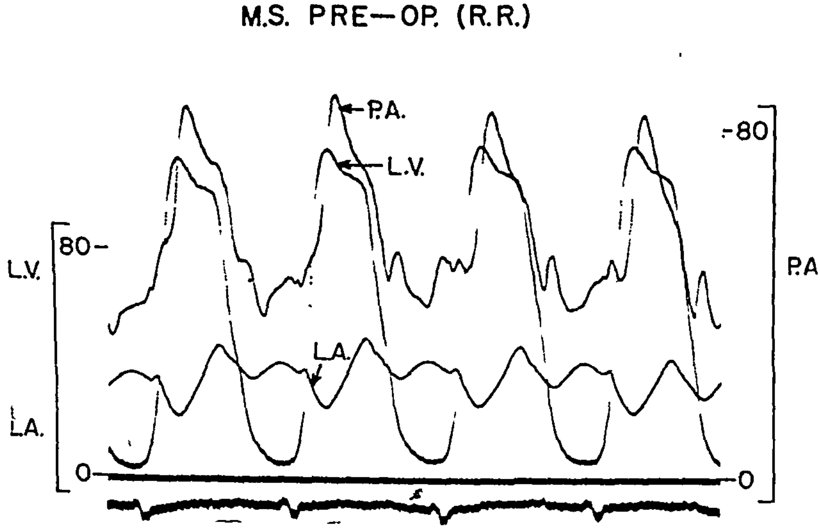


FIGURE 2: Left heart exercise curves in R. R. pre-operatively. The mean diastolic left atrial-left ventricular gradient is 24 mm. Hg. Paper speed is 75 mm. per second.

at the upper limit of normal at rest, Fig. 3. During exercise minimal residual pulmonary hypertension developed. Left heart catheterization at this time demonstrated a mean diastolic gradient of 3 mm. Hg., Fig. 4; on excercise the gradient increased to 6 mm. Hg., Fig. 5. The cardiac output data during the latter study are illustrated in Table I. The close

TABLE I
CARDIAC OUTPUT DATA
R.R. 10/24/56 B.S.A. 1.55

Output Number	Cardiac Index (L./Min./M.² B.S.A.)	Oxygen Consumption (ml./Min./M.² B.S.A.)	A-V Difference (Vol. Per Cent)	R
1.	3.91	121	3.1	.82
2.	3.65	124	3.4	.82
3. (3 Min.)	4.77	257	5.4	.85 (exer.)
4. (7 Min.)	4.95	272	5.5	.97 (exer.)
5.	3.81	118	3.2	.85
6.	3.87	120	3.1	.88
7. (11 Min.)	4.47	259	5.8	.96 (exer.)

Table I: Cardiac output data in R.R. one month after surgery. Outputs 1 and 2 are the resting outputs during right heart catheterization; output 6 is the resting output during combined heart catheterization. The agreement in cardiac index, oxygen consumption, arteriovenous difference and respiratory quotient is excellent.

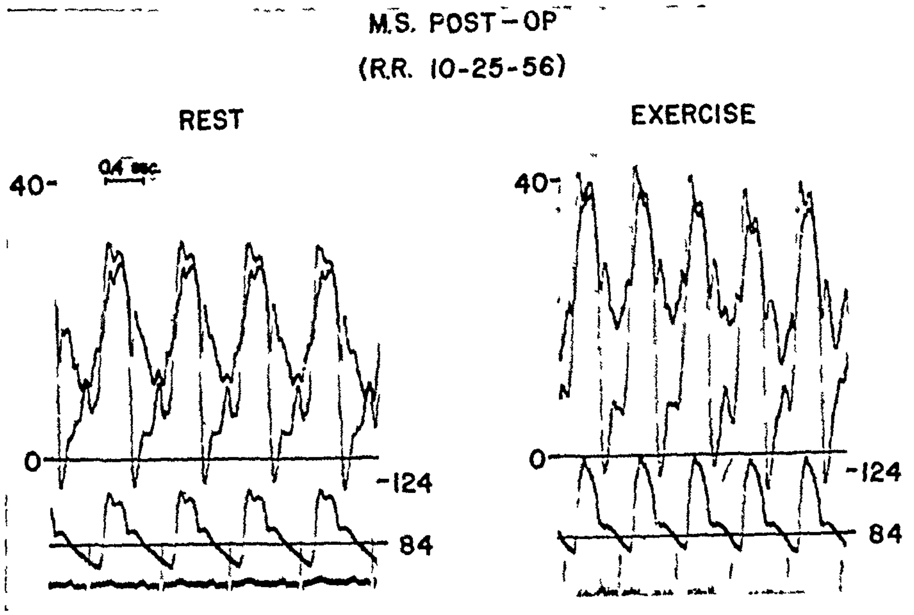


FIGURE 3: Post-operative right heart catheterization data in R. R. Mild pulmonary hypertension is present only during exercise. Study performed October 24, 1956.

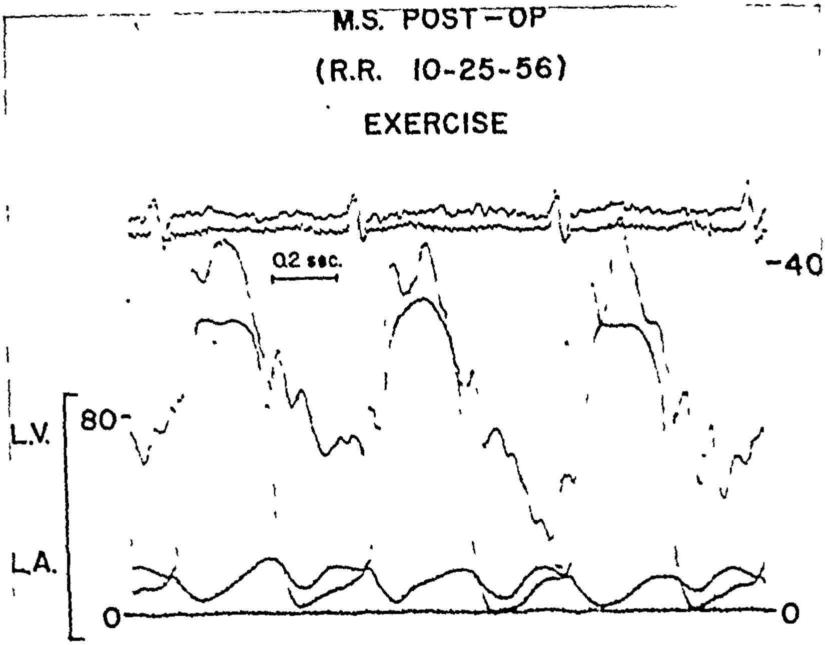


FIGURE 4: One month after surgery the resting mean diastolic left atrial—left ventricular gradient is 3 mm. Hg. at rest. (R. R.) Study performed October 24, 1956.

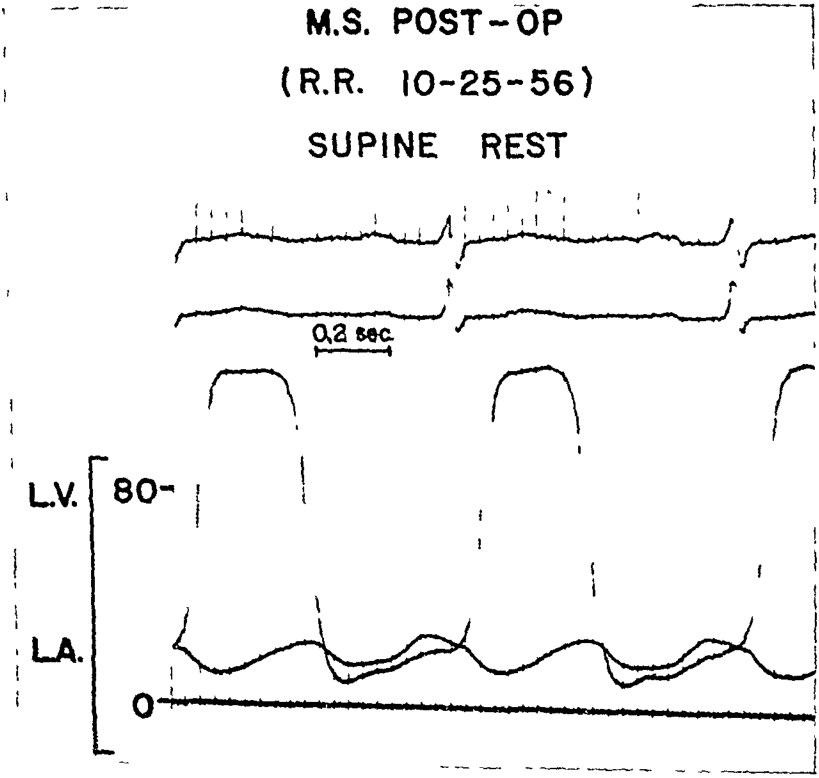


FIGURE 5: During exercise the gradient rises to 6 mm. Hg. Study performed October 24, 1956.

correlation between outputs 1, 2 and 5 during right heart catheterization and output 6 during combined right and left heart catheterization is readily noted. The pre- and post-operative catheterization findings are summarized in Tables II and III.

Pulmonary hypertension secondary to pulmonary vascular disease and to mitral valve block is demonstrated in Figures 6-14. The patient is D.D. Right heart catheterization before surgery shows marked pulmo-

TABLE II
CARDIAC OUTPUT DATA R. Ros. (Rest)

Date	B.S.A. (M.²)		Cardiac Output (Total-/M.²)		S.V. (ml./beat)	O_2 Consumption (Total-/M.²)		A-V (Vol. Per Cent)	R
7/ 5/56	1.63	R	5.43	3.33	57	201	123	3.7	.82
		R	4.90	3.01	57	191	117	3.9	.84
10/24/56	1.55	R	6.06	3.91	76	188	121	3.1	.82
		R	5.65	3.65	72	192	124	3.4	.82
		R	5.90	3.81	70	183	116	3.2	.85
		C	6.00	3.87	66	186	120	3.1	.88

Table II: Resting cardiac outputs in R.R. pre-operative, and one month after commissurotomy. "R" refers to right heart catheterization; "C" refers to combined heart catheterization. The output has risen after surgery.

TABLE III
HEMODYNAMIC DATA R. Ros.

Date		P.C. m	P.A. s/d,m	R.V. s/d	R.A. m	B.A. s/d,m	L.V. s/d	L.A. m	L.A.-L.V. Diast. Grad.
7/ 5/56	R	20	50/26,34	50/2	2	121/66,89			
	Ex.		87/49,61	86/5		135/73,93			
	C.S.		44/27,32	45/2			100/8	23	16
	Ex.		73/43,55				112/9	38	24
10/24/56	R		27/12,17	27/3	2	118/66,86			
	Ex.		36/19,25	38/3		130/70,95			
	C.S.		31/13,21				114/13	14	3
	Ex.		38/20,26				125/13	14	6

Table III: Hemodynamic pressure data in R.R. The marked fall in pulmonary artery pressure one month after surgery suggests that mitral block was the major factor causing pulmonary hypertension. The marked reduction in the atrio-ventricular gradient after surgery is noteworthy. "R" refers to right heart catheterization. "C.S." refers to combined heart catheterization, supine.

nary hypertension at rest, with a further rise during exercise, Fig. 6. The left atrial—left ventricular gradient at rest is 13 mm. Hg., Fig. 7. The operating room studies are pictured in Figs. 8 and 9. One month after surgery pulmonary hypertension persists at rest and during exercise, Fig. 10, despite almost complete abolition of the left atrial—left ventricular mean diastolic gradient both at rest and exercise, Fig. 11. A further fall in right heart pressures is noted 10 months after commis-

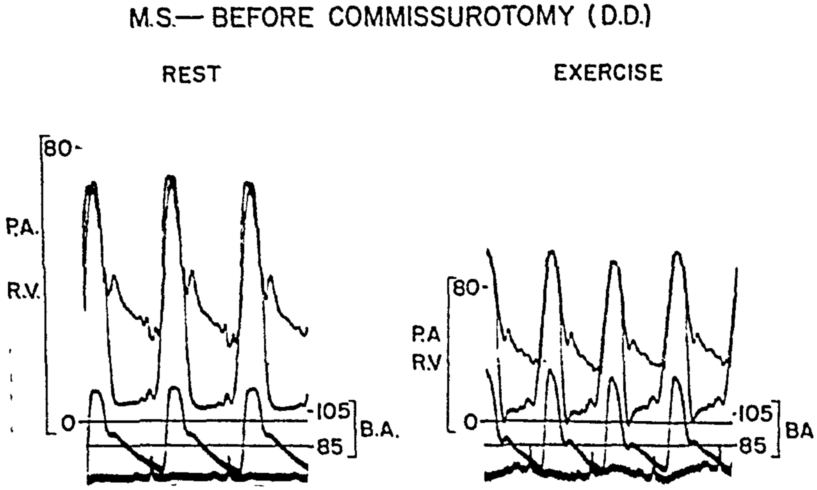


FIGURE 6: Right heart Catheterization data in D. D., pre-operatively. There is marked pulmonary hypertension at rest with a further increase during exercise.

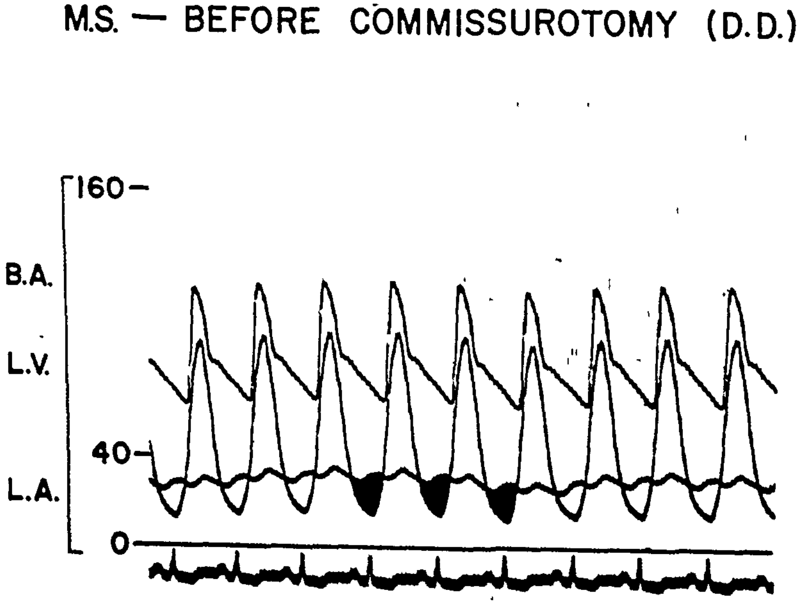


FIGURE 7: Pre-operative left heart catheterization data in the same patient. The left atrial hypertension and mean diastolic left atrial—left ventricular pressure gradient is readily noted.

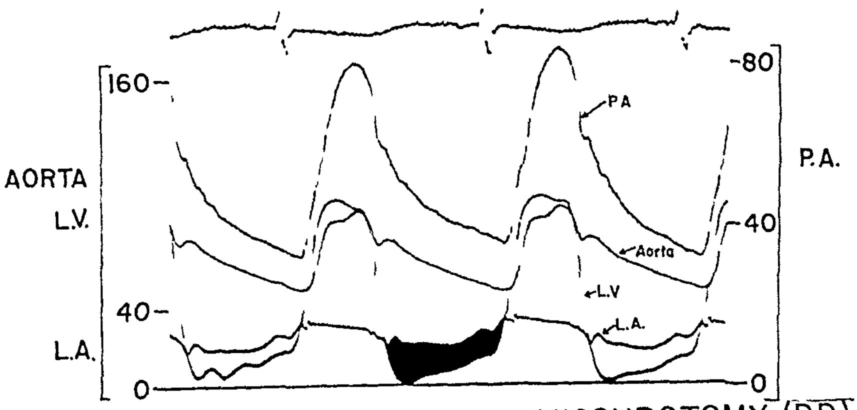
surotomy, Fig. 12, at which time the mean diastolic mitral gradient is 1 and 3 mm. Hg. at rest and exercise respectively, Fig. 13 and 14. The overall catheterization data is shown in Tables IV and V.

More complete regression of pulmonary vascular disease is demonstrated by the data in Tables VI and VII in J. V.

The hemodynamic effects of pulmonary vascular disease and recurrent mitral stenosis are given in tables VIII and IX, and Figures 15-17 in S. B. Moderately severe mitral insufficiency was produced during commissurotomy. Despite marked reduction in the mean diastolic gradient and despite a normal left ventricular end-diastolic pressure (and therefore absence of left ventricular failure) marked pulmonary hypertension both at rest and exercise was noted one month after surgery. One year after surgery, the restenosis of the mitral valve was accompanied by slight elevation of the level of pulmonary hypertension again in the ab-

MS—O.R. PRESSURE BEFORE COMMISSUROTOMY (D.D.

FIG. 8



M.S.—O.R. PRESSURE AFTER COMMISSUROTOMY (D.D.)

FIG. 9

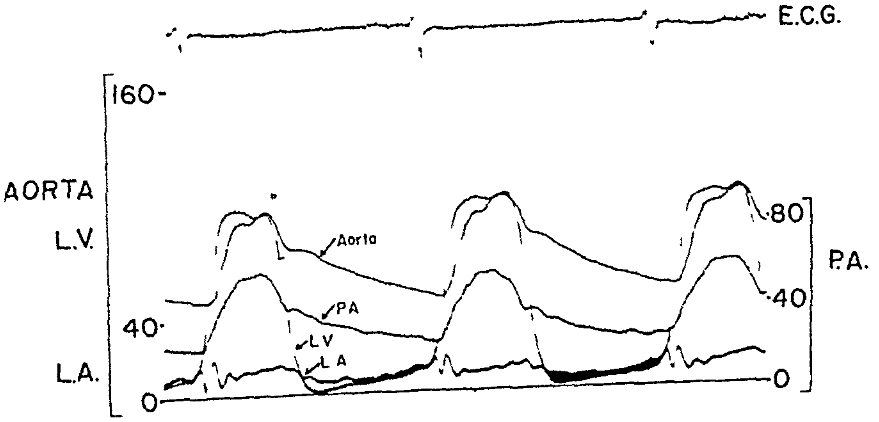


Figure 8: Operating room pre-commissurotomy pressures in D. D.—*Figure 9:* Operating room post-commissurotomy pressures in D. D. The marked decrease in the diastolic gradient is readily seen.

TABLE IV
CARDIAC OUTPUT DATA D. Dix (Res)

Date	B.S.A. (M.²)		Cardiac Output (Total-/M.²)		S.V. ml./beat)	O_2 Consumption (Total-/M.²)		A-V (Vol. Per cent)	R
4/26/56	1.67	R	3.10	1.86	52	208	125	6.7	.93
		R	3.30	1.98	50	214	128	6.5	.73
6/28/56	1.61	R	4.02	2.49	61	201	125	5.0	.77
		R	3.71	2.31	56	204	127	5.5	.77
		R	4.09	2.54	....	217	135	5.3	.76
3/14/57	1.73	R	3.83	2.21	56	207	120	5.4	.69
		C	4.19	2.42	59	218	126	5.2	.72
		C	4.37	2.53	64	223	129	5.1	.72

Table IV: Resting cardiac outputs in D.D., before surgery and one and ten months after commissurotomy. There is a clear rise in flow after surgery.

TABLE V
HEMODYNAMIC DATA D. Dix.

Date		P.C. m	P.A. s/d,m	R.V. s/d	R.A. m	B.A. s/d,m	L.V. s/d	L.A. m	L.A.-L.V. Diast. Grad
4/26/56	R	19	75/27,42	75/5	3	117/70,84			
	Ex.		103/36,57	102/11		114/66,87			
	C.S.		98/34,55				95/ 9	21	13
6/28/56	R	8	52/18,30	54/5		119/67,87			
	Ex.		71/26,42	72/5		131/63,89			
	C.S.		68/22,36				114/11	10	1
	Ex.		91/37,55				127/13	14	4
3/14/57	R	15	33/10,19	33/4		125/64,90			
	Ex.		52/19,30	52/3		142/70,97			
	C.S.		45/13,24	45/4			127/10	11	1
	Ex.		62/21,36	62/5			132/ 9	9	3

Table V: Pressure data in D.D. before and after surgery.

sence of an elevation in the left ventricular end diastolic pressure. The post-operative mitral insufficiency is noted in Figs. 16 and 17.

Pulmonary hypertension secondary to left ventricular failure with an elevation of the left ventricular end-diastolic pressure is demonstrated in Fig. 18 and Tables X and XI. Mitral stenosis was not found during the combined heart catheterization or during the post-mortem examina tion one month later. The elevation in left ventricular end-diastolic, left atrial mean and mean pulmonary artery wedge pressure all are most compatible with pulmonary hypertension secondary to left ventricular failure.

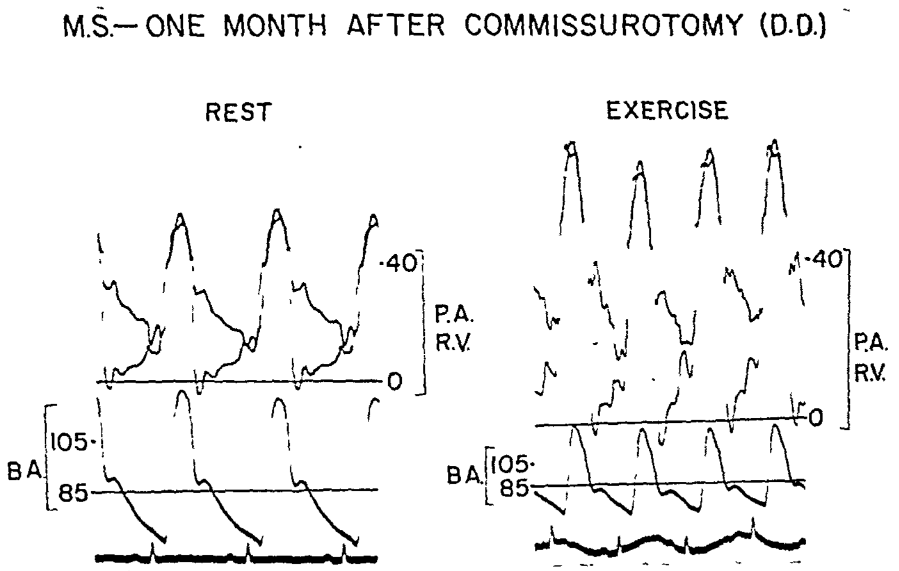


FIGURE 10: Right heart curves in D. D. one month after surgery. There has been a decrease in the level of pulmonary artery pressure at rest and exercise, but marked pulmonary hypertension persists.

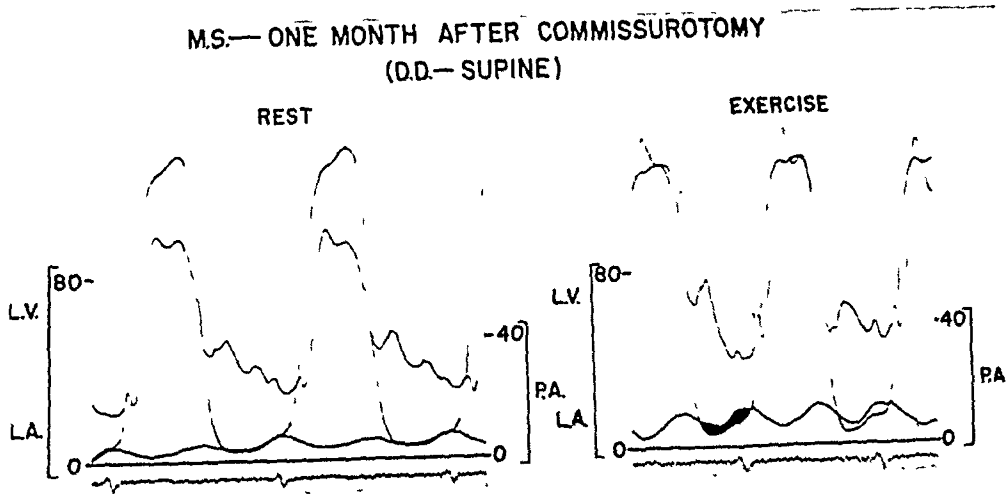


FIGURE 11: Left heart catheterization data in D. D. one month after commissurotomy. The diastolic gradient is 1 mm. Hg. at rest and 4 mm. Hg. during exercise. The left ventricular end-diastolic pressure is normal throughout.

FIG. 12

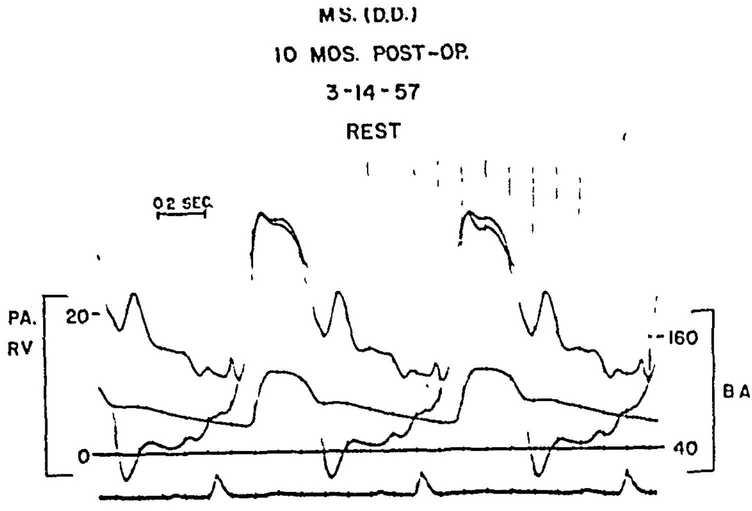


FIG. 13

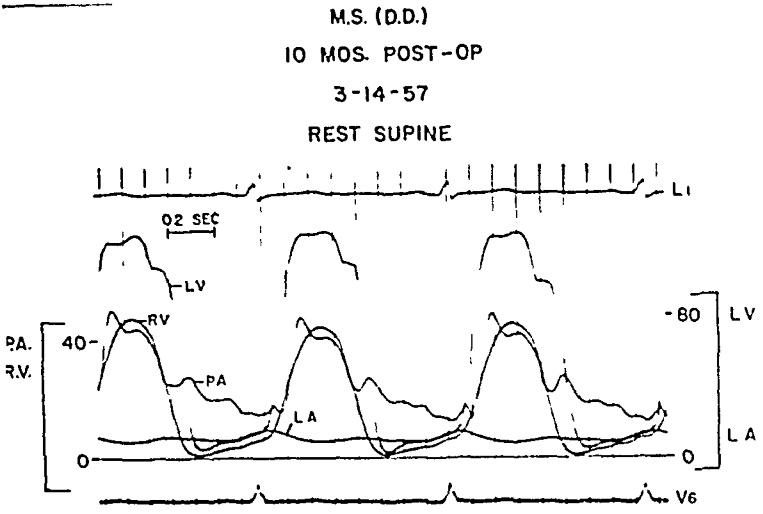


FIG. 14

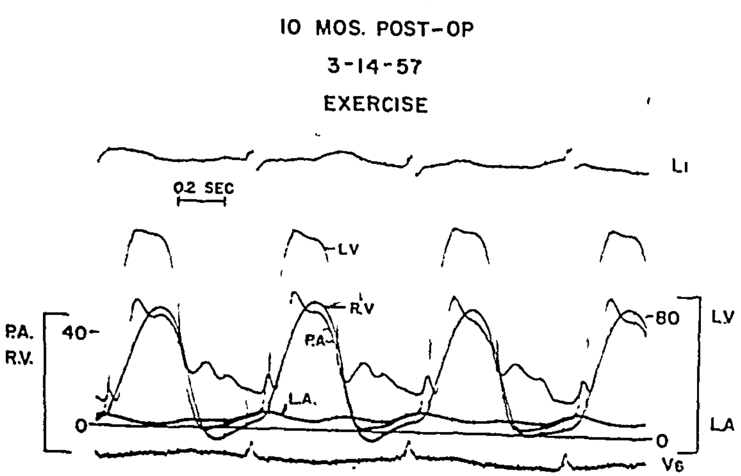


Figure 12: Ten months after surgery a further fall in pulmonary artery pressure is noted in D. D.—*Figure 13:* Right and left heart curves in D. D., at rest supine ten months after commissurotomy. The resting gradient is 1 mm. Hg.—*Figure 14:* The exercise gradient is 3 mm. Hg., D. D.

TABLE VI
CARDIAC OUTPUT DATA J. Van. (Rest)

Date	B.S.A. (M.^{2})		Cardiac Output (Total-/M.^{2})		S.V. (ml./beat)	O^2 Consumption (Total-/M.^{2})		A-V (Vol. Per Cent)	R
4/12/56	1.56	R	3.82	2.45	58	193	124	5.1	.86
		R	4.00	2.56	59	196	126	4.9	.87
6/ 2/56	1.49	R	3.64	2.44	49	200	134	5.5	.80
		R	3.70	2.49	47	200	134	5.4	.89
7/12/56	1.52	R	4.30	2.83	48	228	150	5.3	.87
		R	4.07	2.68	51	203	134	5.0	.88
4/23/57	1.55	R	4.30	2.77	52	202	130	4.7	.78
		R	4.60	2.97	57	230	148	5.0	.78

Table VI: Resting cardiac outputs in J.V. before commissurotomy and one, two and twelve months after surgery. The postoperative rise in output is again to be noted.

TABLE VII
HEMODYNAMIC DATA J. Van.

Date		P.C. m	P.A. s/d,m	R.V. s/d	R.A. m	B.A. s/d,m	L.V. s/d	L.A. m	LA.-L.V. Diast. Grad.
4/12/56	R	19	38/18,26	38/4	3	116/70,85			
	Ex.		87/43,60	87/5		159/90,115			
	C.S.		40/17,26	42/4			92/11	19	8
	Ex.		87/37,54				108/13	29	13
6/ 2/56	R	7	26/10,17	27/2		120/74,97			
	Ex.		37/18,24	39/2		155/85,112			
7/12/56	R	4	25/11,14	25/1		121/75,92			
	Ex.		32/15,18	34/2		140/80,100			
4/23/57	R	3	16/ 6,10			124/69,89			
	Ex.		27/10,16			155/75,104			
	C.S.		16/ 6, 9				105/ 7	7	1
	Ex.		25/ 9,13				125/ 7	7	2

Table VII: Right and left heart hemodynamic data in J.V. before and after surgery.

TABLE VIII
CARDIAC OUTPUT DATA S. Bri. (Rest)

Date	B.S.A. (M.²)		Cardiac Output (Total-/M.²)		S.V. (ml./beat)	O_2 Consumption (Total-/M.²)		A-V (Vol. Per Cent)	R
2/ 9/56	1.65	R	4.13	2.51	48	186	112	4.5	.87
		R	4.09	2.48	47	180	109	4.4	.90
3/31/56	1.61	R	3.74	2.32	43	179	111	4.8	.84
		R	3.40	2.11	51	170	106	5.0	.85
2/21/57	1.66	R	3.20	1.93	46	176	106	5.5	.75
		R	2.93	1.77	41	170	102	5.8	.78

Table VIII: Resting outputs in S.B. The outputs have fallen sharply subsequent to the inadvertent production of mitral insufficiency at surgery.

TABLE IX
HEMODYNAMIC DATA S. Bri.

Date		P.C. m	P.A. s/d,m	R.V. s/d	R.A. m	B.A. s/d,m	L.V. s/d	L.A. m	L.A.-L.V. Diast. Grad.
2/ 9/56	R	24	63/28,41	61/2		110/64,85			
	Ex.		127/55,77			133/71,94			
	C.P.					116/69,89	98/ 4	20	12
3/31/56	R		51/28,37		2	114/63,79			
	Ex.		87/40,60			108/64,84			
	C.P.					113/68,89	106/10	14	3
2/21/57	R		65/25,40	65/3	0	109/66,85			
	Ex.		134/54,84	134/17	9[a]	146/84,117			
	C.P.						112/11	16	9

a. Z point = 14 mm. Hg.

Table IX: Right and left heart pressure levels in S.B. "C.P." refers to combined heart catheterization, prone.

Discussion

Right heart catheterization cannot be relied upon to readily separate pulmonary vascular disease, mitral valve block, and left heart failure as etiological factors in the production of pulmonary hypertension. Pulmonary vascular disease can theoretically be separated from the other mechanisms via the pulmonary artery wedge pressure.[5] However normal pulmonary artery wedge pressure has been recorded in subjects with physiologically and surgically proven mitral stenosis in our laboratory. The pulmonary artery wedge pressure in Fig. 19 is 12 mm. Hg., a level within normal limits. Figure 20 illustrates the left heart catheterization curves.

FIG. 15

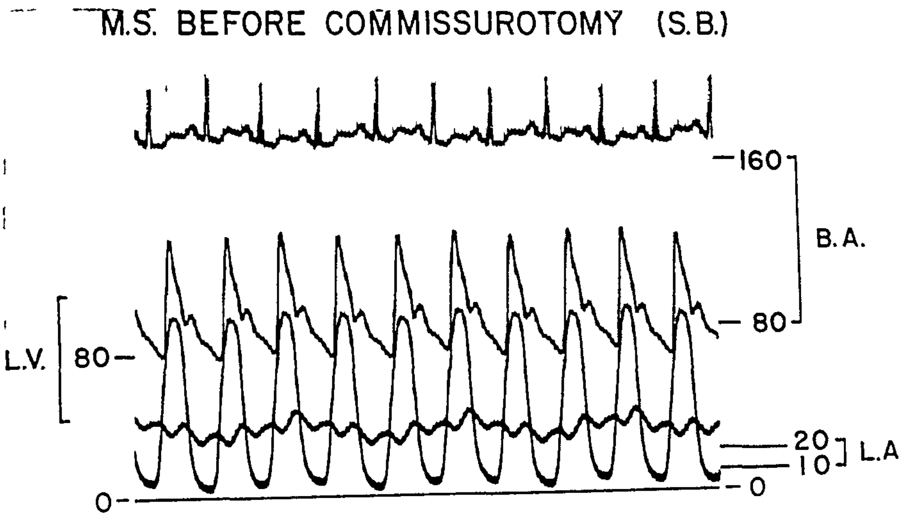


FIG. 16

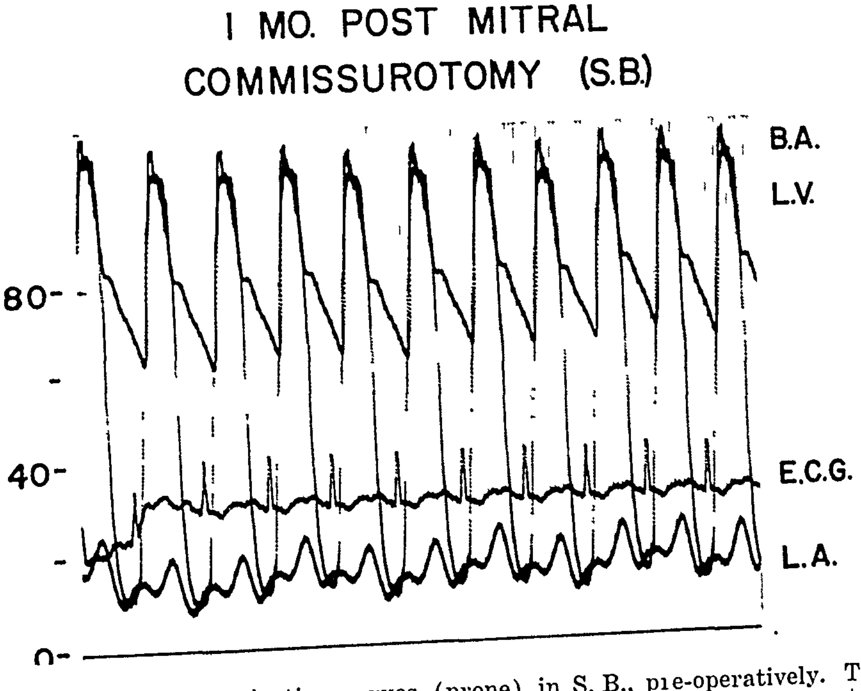


Figure 15: Left heart catheterization curves (prone) in S. B., pre-operatively. There is no evidence of mitral insufficiency.—*Figure 16:* One month after commissurotomy. The diastolic gradient has been reduced to 3 mm. Hg., prone position. The left atrial curve is suggestive of mitral insufficiency.

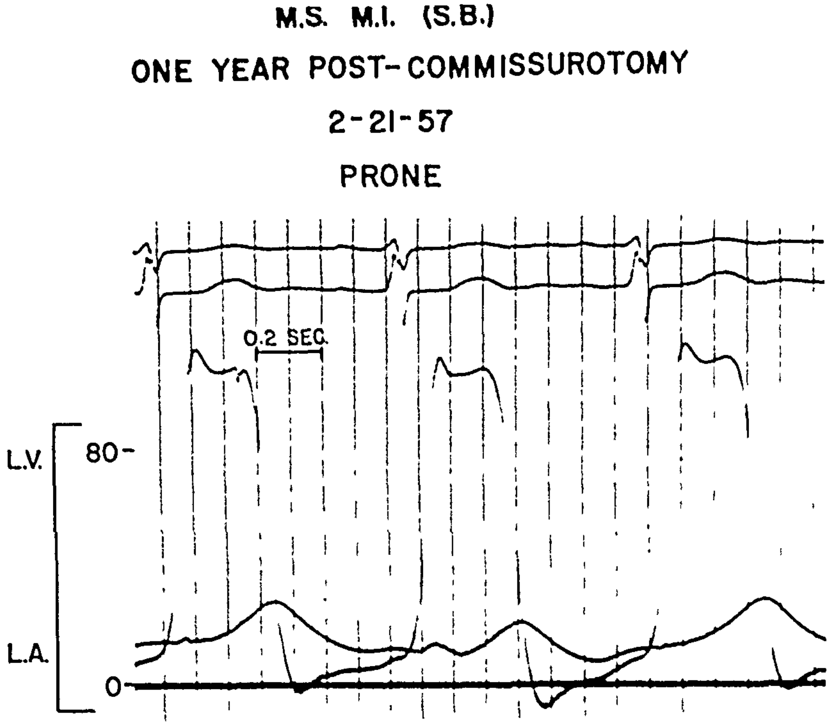


FIGURE 17: Left heart curves one year after surgery in S. B. A mean diastolic atrioventricular gradient has reappeared.

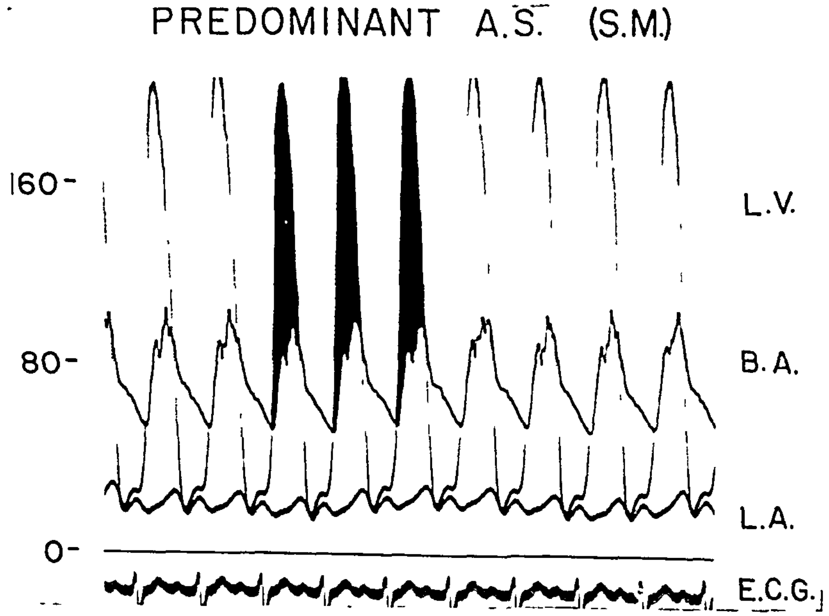


FIGURE 18: Severe aortic stenosis in S. M. The left atrial mean and left ventricular end-diastolic pressures are markedly elevated.

TABLE X
CARDIAC OUTPUT DATA S. Mar.

Date	B.S.A. (M.²)		Cardiac Output (Total-/M.²)		S.V. (ml./beat)	O_2 Consumption (Total-/M.²)		A-V (Vol. Per Cent)	R
3/17/56	1.47	R	3.60	2.45	39	263	179	7.3	.84
		R	3.40	2.31	36	256	174	7.5	.79
		Ex.	4.03	2.74	32	512	348	12.7	.93
		Ex	3.59	2.44	28	481	327	13.4	1.00

Table X: Rest and exercise outputs in S.M., a patient with severe aortic stenosis.

There is a significant mean diastolic left atrial—left ventricular gradient; at surgery the mitral valve was found to be markedly stenotic. The presence of normal pulmonary artery wedge pressure does not signify the absence of mitral valve block.

On the other hand, combined right and left heart catheterization permits direct demonstration of the presence or absence of mitral valve block and left ventricular failure by determination of the atrio-ventricular diastolic gradient and the left ventricular end-diastolic pressure. Concomitant determination of pulmonary artery pressure and cardiac output permits an approximate evaluation of pulmonary arteriolar resistance. Elevated pulmonary resistance levels are suggestive in turn of pulmonary vascular disease. It is thus possible to adduce evidence for any or all of the three projected mechanisms for the production of pulmonary hypertension by means of right and left heart catheterization. In any one patient however the quantitative contribution of these abnormalities to the degree of pulmonary hypertension may be difficult to evaluate.

The catheterization data in D. D. are of considerable interest. There is a large left atrial—left ventricular gradient at rest, 13 mm. Hg. De-

TABLE XI
HEMODYNAMIC DATA S. Mar.

Date		P.C. m	P.A. s/d,m	R.V. s/d	R.A. m	B.A. s/d,m	L.V. s/d	L.A. m	L.V.-B.A. Syst. Grad.
3/17/56	R	20	44/25,31		1	98/62,78			
	Ex.		88/46,59			111/60,78	207/26	23	68
	C.P.								

Table XI: Pressure studies demonstrate marked elevation of left atrial mean pressure and of the left ventricular end-diastolic pressure.

spite almost complete abolition of the gradient, pulmonary hypertension persisted one month after surgery. In the presence of a normal left ventricular end-diastolic pressure, residual pulmonary vascular disease emerges as the most likely explanation of the post-operative hypertension in the lesser circuit. The cardiac output data at rest (Table II)

FIG. 19

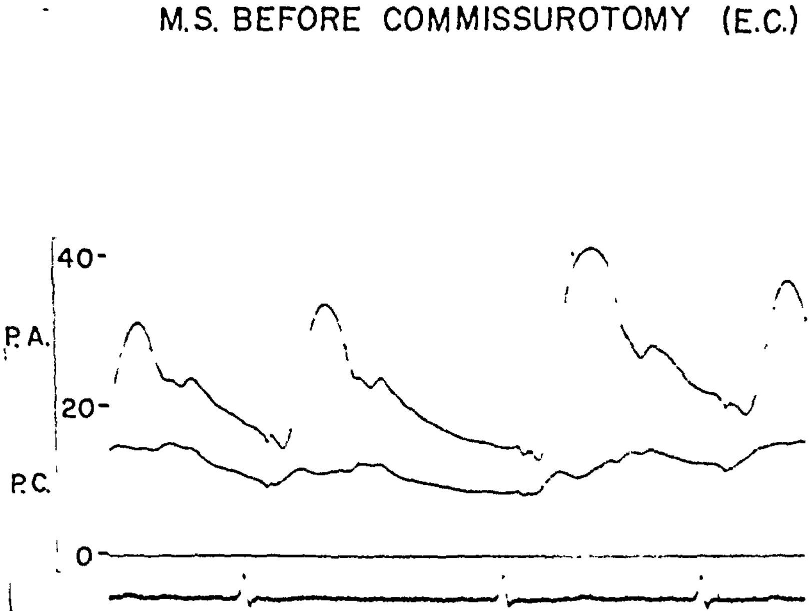


FIG. 20

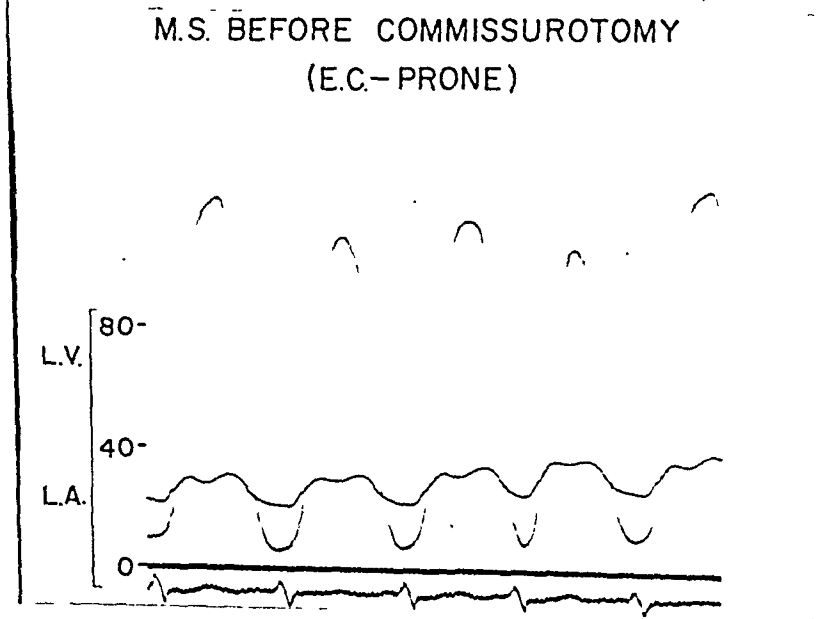


Figure 19: Pulmonary "capillary" pressure in E.C. The mean pressure is 12 mm. Hg., at the upper limit of normal.—*Figure 20:* There is an obvious significant mean diastolic left atrial—left ventricular gradient. Tight mitral stenosis was found at surgery.

demonstrate the rise in flow after commissurotomy. No recurrence of mitral stenosis was noted ten months after surgery.

Complete restoration of pulmonary artery pressure to normal levels over the course of one year after surgery is demonstrated in Table VII. The most marked fall in pulmonary artery pressure occurred in the immediate post-operative period suggesting that mitral block was the major cause of pulmonary artery pressure elevation. The continued fall over the course of one year illustrates the effect of resolution of pulmonary vascular disease. A gradual, but slight rise in cardiac output was noted over this period.

Multiple catheterization studies in S.B. demonstrate the hemodynamic effects of the surgical production of mitral insufficiency. A progressive fall in cardiac index developed after surgery. The pre-operative gradient (12 mm. Hg) fell to 3 mm. Hg. The persistent pulmonary hypertension at this time may at first glance be ascribed to pulmonary vascular disease. It is possible that severe mitral insufficiency may also contribute to pulmonary hypertension because of elevation of mean left atrial pressure secondary to the mitral insufficiency. The 9 mm. Hg gradient one year after surgery suggests restenosis of the mitral valve. In the presence of mitral insufficiency, the flow across the valve in diastole is increased. The diastolic gradient is thus larger (for a given sized mitral valve) than it

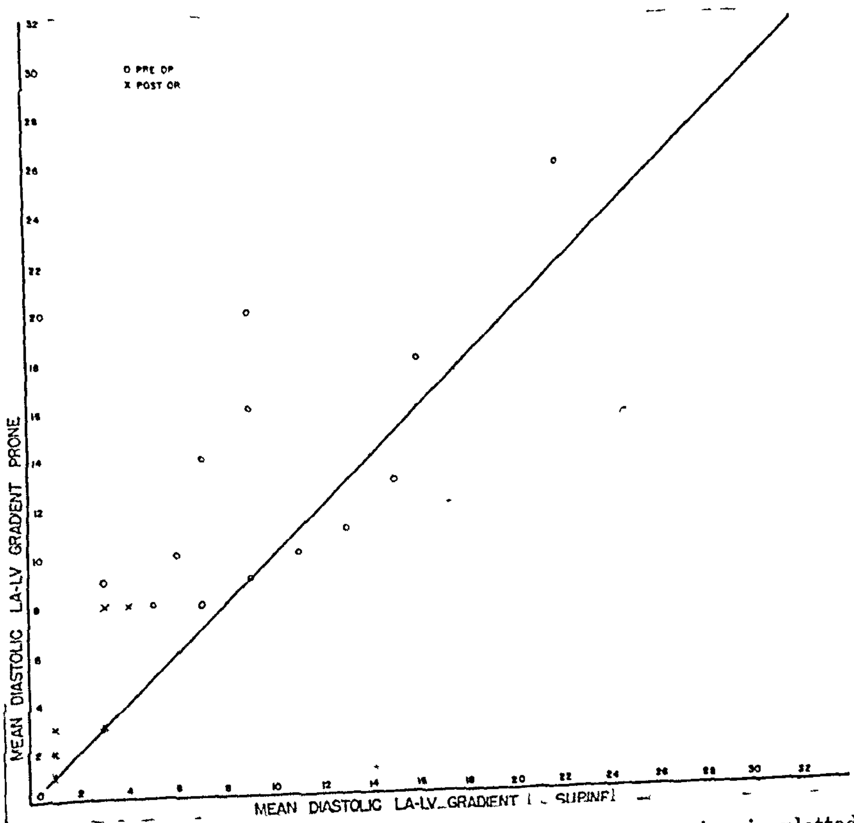


FIGURE 21: The mean diastolic atrio-ventricular gradient supine is plotted on the abcissa; the prone gradient is on the ordinate. The deviation from the 45° line of identity is to be noted.

would be in the absence of insufficiency; the gradient magnitude must therefore be interpreted carefully when significant insufficiency is present.

The data in S.M. illustrate the production of pulmonary hypertension by left heart failure.

One further point deserves emphasis. The mean diastolic left atrial - left ventricular gradient varies in the prone and supine positions. This is illustrated in Fig. 21. The prone gradient is plotted on the ordinate and the gradient supine is plotted on the abcissa. The continuous line has been drawn at a 45 degree angle. If the gradients were identical in the two positions, the points would fall along the theoretical straight line. The wide divergence from this line is readily seen. Since various laboratories perform left heart catheterization in different positions[6, 8] (prone or supine) difficulties in gradient interpretation can readily arise.

SUMMARY

Pulmonary vascular disease, mitral valve block, left heart failure, or any combination of these factors may cause pulmonary hypertension. Right heart catheterization alone, in rheumatic heart disease, cannot differentiate among these possibilities. Right and left heart catheterization is of great aid, however, in resolution of the problem. Five cases are discussed to illustrate the value of combined heart catheterization.

Drs. Robert S. Litwak, Francis Cooke, DeWitt Daughtry and Myron Segal performed mitral commissurotomy as indicated in these patients.

RESUMEN

La enfermedad pulmonar vascular, el bloqueo de la válvula mitral, el desfallecimiento cardiaco izquierdo o cualquiera de las combinaciones de estos factores, puede causar la hipertensión pulmonar.

El cateterismo del lado derecho del corazón solo, en la enfermedad cardiaca reumática no puede diferenciar estas posibilidades.

La cateterización derecha e izquierda es de gran ayuda, sin embargo, para resolver el problema. Se discuten cinco casos para ilustrar el valor de la cateterización combinada del corazón.

RESUME

L'atteinte de l'artère pulmonaire, l'obstruction de la valvule mitrale, l'arrêt du coeur gauche, ou toute combinaison de ces trois facteurs peut être à l'origine d'hypertension pulmonaire. Dans le rhumatisme cardiaque, le cathétérisme du coeur droit seul ne peut pas distinguer ces diverses éventualités. Le cathétérisme des cavités droites et gauches est cependant d'un grand secours à ce point de vue. Les auteurs mettent en discussion cinq observations qui illustrent la valeur du cathétérisme cardiaque combiné.

ZUSAMMENFASSUNG

Pulmonale Gefässerkrankung, Mitralklappenblock, Versagen des linken Herzens oder irgendeine Kombination dieser Faktoren kann die Ursache

für einen pulmonalen Hochdruck sein. Eine Katheterisierung des rechten Herzens allein kann bei rheumatischer Herzerkrankung nicht zwischen diesen Möglichkeiten unterscheiden. Eine Katheterisierung des rechten und linken Herzens ist jedoch von grosser Hilfe für die Lösung des Problemes. 5 Fälle werden besprochen, um den Wert der kombinierten Herz-Katheterisierung zu veranschaulichen.

REFERENCES

1 Harvey, R. M., Ferrer, M. I., Samet, P., Bader, R. A., Bader, M. E., Cournand, A. and Richards, D. W.: "Mechanical and Myocardial Factors in Rheumatic Heart Disease with Mitral Stenosis," *Circulation*, 11:531, 1955

2 Ferrer, M. I., Harvey, R. M., Wylie, R. H., Himmelstein, A., Lambert, A., Kuschner, M., Cournand, A. and Richards, D. W.: "Circulatory Effects of Mitral Commissurotomy with Particular Reference to Selection of Patients for Surgery," *Circulation*, 12:7, 1955.

3 Fisher, D. L.: "The Use of Pressure Recordings Obtained at Transthoracic Left Heart Catheterization in the Diagnosis of Valvular Disease," *J. Thoracic Surg.*, 30:379, 1955.

4 Gordon, A. J., Braunwald, E. and Ravitch, M. M.: "Simultaneous Pressure Pulses in the Human Left Atrium, Ventricle, and Aorta," *Circulation Research*, 2:432, 1954.

5 Hellems, H. K., Haynes, F. W. and Dexter, L.: "Pulmonary Capillary Pressure in Man," *J. Applied Phys.*, 2:24, 1949.

6 Fisher, D. L. and McCaffrey, M. M.: "Right and Left Atrium Needle Puncture for Simultaneous Right and Left Heart Catheterization." Presented at the 29th Scientific Sessions, *American Heart Association*, Ocober 26-29, 1956, Cincinnati, Ohio.

7 Wood, E. H., Sutterer, W., Swan, H. J. C. and Helmholz, H. F.: "The Technique and Special Instrumentation Problems Associated with Catheterization of the Left Side of the Heart," *Proc. Staff Meetings of the Mayo Clinic*, 31:108, 1956.

8 Goldberg, H., Dickens, J., Rabex, G. and Hayes, E., Jr.: "Simultaneous (Combined) Catheterization of the Left and Right Heart," *Am. Heart Jour.*, 53:579, 1957.

Myocardial Revascularization by Means of Cardiopneumopexy and Ivalon Graft

FRANKLIN R. SMITH, M.D., F.C.C.P., HOWARD PYFER, M.D.,
WAYNE GARRETT, M.D., J. BROOKS DUGAN, M.D. and DAVID McINTYRE, B.S.
Seattle, Washington

Cardiopneumopexy will aid and augment natural processes in revascularizing the ischemic myocardium. By cardiopneumopexy we mean grafting the left lung to the heart after removal of the twin barriers of pericardium and epicardium. Lezius, the German investigator, whose death from coronary occlusion occurred all too early in life, initiated this concept in 1937. We worked in our laboratory unaware of Lezius' work until well into our explorations. Then, upon becoming acquainted with his ideas, integrated his thoughts into our program and investigated the whole concept in detail over the past five years.

Our current concept of the technique of cardiopneumopexy is wide incision of the pericardium from apex to the base of the heart, phenol epicardiolysis, asbestos poudrage and suturing of the lung to the myocardium over as broad an area as possible. Usually the lingula is used. In some instances the lung is sutured to the inner surface of the pericardium when sutures through a scarred infarct of the heart might result in a tear into the chamber of the ventricle, as we experienced once clinically.

Coronary heart disease being the leading single cause of death in the United States, killing annually as many people as all forms of cancer, one-quarter of a million individuals, myocardial revascularization is an appealing target for surgical research. Since one out of four patients dies at the time of his first attack and of the survivors 10 per cent die each succeeding year, giving such a patient a life expectancy of only four and one half years if he survives the initial attack, more must be offered to these patients than the current traditional medical treatment.

Our surgical goal is to relieve angina, to lengthen life and to return the patient to productive labor and a satisfactory position in society.

Approximately 187 dogs have been utilized in all phases of this investigation. Nineteen patients have undergone cardiopneumopexy in the past three years with two hospital deaths and two deaths occurred subsequently, one at three months and one at six months.

The two deaths, from ventricular fibrillation, that occurred post-operatively in the hospital were due to the problem of selection of cases, a question that experience now has corrected. The patient who died three months postoperatively had coronary artery disease that had advanced to the stage where revascularization was of little value; this degree of coronary disease we now feel cannot always be predicted by medical means before surgery. The man who died six months postoperatively had a lone predominate coronary artery which was 95 per cent occluded at

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the time of surgery; this anatomic variation sealed his fate in the face of atherosclerosis. The others generally are doing well and we are encouraged, although at least another ten years are needed to fully evaluate this procedure. Angina has been substantially helped in all but one. In this one individual there is a considerable amount of fibrous and emphysematous lung disease which may be a factor in his myocardial anoxia.

All of the patients have had extensive medical profiles by internists and the majority have been seen by the same psychiatrist* to evaluate carefully the psychological and psychiatric aspects. The psychiatrist feels that he can frequently predict which patients will eventually develop coronary heart disease. He has been of great aid in separating psychic from somatic heart pain and in evaluating what part of the postoperative relief of angina is due to suggestion and what due to the surgery. His opinion has augmented information given us by devices like the treadmill.

We have not chosen to operate on patients over the arbitrary tissue age of 60 years, patients who have had concomitant serious vascular disease such as cerebrovascular accidents, intermittent claudication or aneurysms, patients who must be maintained on digitalis because of inadequate cardiac musculature or patients who have had a myocardial infarct more recently than six months.

Since virtually all coronary occlusions occur within the two main arteries or their primary branches, endarterectomy to remove the obstructing atherosclerotic material is an intriguing approach. Unfortunately, currently it is not technically feasible. So, we have postulated that to bridge the defect would be next best direct attack on the problem. We felt that an Ivalon graft could serve as a bridge over the occlusion. As a first step in that direction, we have sutured a tapered Ivalon graft to the subclavian artery and inserted the other end into a major coronary artery. Dogs have survived acute coronary occlusion after this procedure but the grafts do not continue to transmit blood. Apparently the peripheral myocardial field becomes obstructed. This work will be concluded in 1958 and then reported. Cardiopneumopexy currently is still the superior surgical technique for coronary insufficiency.

There is available a technique of radiographic visualization of the coronary arteries in vivo that brings to the horizon the possibility of delineating the area of obstruction in the coronary artery as neatly as we can in bronchiectasis by the use of iodized oil. This would accurately direct surgical attack on an offending vessel, when and if such a method becomes surgically feasible for patients.

SUMMARY

Coronary heart disease is the leading single cause of death. Current methods of medical therapy are not adequate. Ancillary surgical aids may be of help in treatment of this disease. Cardiopneumopexy has been demonstrated in the laboratory and clinically to be an encouraging method of

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*Doctor Dugan's untimely death May 19, 1957, in his early thirties was a loss to the profession of a brilliant psychiatrist who had a solid basis in clinical medicine.

stimulating extracoronary and intracoronary collateral circulation. Ivalon grafts to by-pass the obstructed area in the coronary artery offer intriguing possibilities for the future. These surgical methods are no panacea; they are offered as actual and potential adjuncts to existing medical programs.

RESUMEN

La causa de muerte que va a la cabeza, es la enfermedad cardiaca coronaria. Los métodos actuales de tratamiento médicos no son adecuados. Los procedimientos quirúrgicos auxiliares pueden ser de utilidad en el tratamiento de esta enfermedad. La cardioneumopexia ha demostrado en el laboratorio y clínicamente también ser un método alentador para estimular la circulación colateral extra e intracoronaria. Los injertos de Ivalón para sortear el área obstruída en la arteria coronaria, ofrecen posibilidades atrayentes para el futuro. Estos métodos quirúrgicos no son una panácea; son ofrecidos como agregados reales y potenciales a los métodos que ya existen.

RESUME

L'atteinte des artères coronaires est la cause principale de la mortalité. Les méthodes courantes de traitement médical ne sont pas suffisantes. L'aide chirurgicale peut être d'un grand secours dans le traitement de cette affection. La cardio-pneumopexie s'est montrée être, au laboratoire et cliniquement, une méthode encourageante pour stimuler la circulation extra-coronarienne et intra-coronarienne collatérale. Les greffes d'"Ivalon" pour pallier à l'obstruction d'un segment de l'artère coronaire offrent des possibilités intéressantes pour l'avenir. Ces procédés chirurgicaux ne sont pas des panacées; ils sont des compléments actifs et efficaces aux possibilités médicales déjà existantes.

ZUSAMMENFASSUNG

Herzkranzgefässerkrankung ist die führende alleinstehende Todesursache. Die gegenwärtige Methode der interen Behandlung ist nicht adaequat. Zustzliche chirurgische Hilfen kõnnen von Wert sein bei der Behandlung dieser Krankheit. Cardiopneumopexie hat sich im Laboratorium und Klinik als ein ermutigendes Verfahren erwiesen zur Reizung der extracoronaren und intracoronaren Kollateral-Zirkulation. Ivalon-Transplantate für einen Kollateralkreislauf des verschlossenen Abschnittes der Coronar-Artherien bieten interessante Möglichkeiten für die Zukunft. Diese chirurgischen Methoden sind kein Allheilmittel; sie bieten sich an als aktuelle und potentielle Zugabe für bestehende interne Behandlungspläne.

BIBLIOGRAPHY

Lezius, A.: "Die Kiensteliche Blut Versorgung des Herzmuskels," *Arch. f. Klin. Chir.*, 189:342, 1937.

Lezius, A.: "Die Anatomischen und Funktionellen Grundlazen der Kienstlichen Blut Versorgung des Herzmuskels durch die Lunge bei Coronorarterienverschluss," *Arch. f. Klin. Chir.*, 191:101, 1938.

Lezius, A.: "Die Behandlung der Angina Pectoris und der Coronarinsuffizienz durch die Kardio-Pneumopexie," *Arch. f. Klin. Chir.*, 267:576, 1951.

Smith, F. R.: "Coronary Artery Collateral Circulation Developed by Heart-Lung Graft," *Anat. Record*, 119:95, 1954.

Smith, F. R.: "The Epicardial Barrier in Surgical Revascularization of the Heart," *West. J. Surg.*, 63:66, 1955.

CURRENT THERAPY

The Editorial Board invites your comment

The Management of the Hypertensive Patient

Considerable advances both in the diagnosis and treatment of hypertension have tended to confuse the management of the hypertensive patient. This discussion will in brief attempt to elucidate the problem.

Diagnosis

The term arterial hypertension implies elevation of both systolic and diastolic levels of pressure; the upper limit of normality being 150/90 mm of mercury. The finding of a persistently elevated diastolic pressure of over 90 mm of mercury is diagnostic of arterial hypertension. In the presence of emotional instability and obesity of the biceps area, increased pressures can be found, but under these circumstances, the elevation in diastolic pressure may not be significant. Recently Masters' has demonstrated that the levels of blood pressure tend to increase with age and the normal standard of 150/90 mm of mercury may have to be revised for the elder age groups.

Elevation of the diastolic pressure is primarily a result of increased peripheral arteriolar resistance due to generalized vasoconstriction or arteriolar narrowing. Elevation of the systolic pressure only may occur clinically and differs hemodynamically from arterial hypertension in that it is caused primarily by decreased distensibility of the aorta due to arteriosclerosis. This condition does not result in increased cardiac work and in general is benign requiring no treatment. Occasional cases of elevated systolic pressures are caused by an increase in cardiac output. (See Table 1)

When the presence of arterial hypertension is established, it is important that attempts to determine its etiology be made. It should be pointed out that while approximately 80 per cent of all cases of hypertension have no known etiology and are thus called "Essential," the remainder may have either a renal, neurogenic, hormonal or vascular etiology. Some of these cases are amenable to treatment and occasionally a dramatic cure of arterial hypertension may occur as a result of thoroughness in tracking down the possible causes of a patient's hypertension. Table 1 classifies the etiological causes of hypertension. As a result of compiling a careful history, doing a thorough physical examination and ordering appropriate laboratory examinations, it is possible to diagnose the etiological cause of hypertension and estimate the severity of the disease. Since the patient's management is determined by these two factors, the importance of this is obvious.

Table 2 summarizes the routine and specialized laboratory tests available as aids in determining the origin of arterial hypertension. The astuteness of the physician in the elaboration of the history and in the performance of the physical examination determines the extensiveness of the laboratory tests required. Obviously not all cases need be subjected to the entire battery of tests enumerated in Table 2.

Clinical descriptions of the various hypertensive syndromes have not been described because it is beyond the scope of this presentation; however, certain precepts concerning some of the syndromes and tests will be presented for the sake of emphasis.

Renal hypertension is commonly preceded by a history of renal disease or a history of an abnormal urinalysis unassociated with hypertension. Recently, the importance of unilateral renal disease as a cause for hypertension has been demonstrated by Howard[2] who has reported impairment in the excretion of sodium and water in an ischemic kidney. Removal of this kidney has resulted in a return to normal blood pressure. Several cases with normal excretory pyelograms have also shown this unilateral impairment of sodium and water excretion and following unilateral nephrectomy normal blood pressures were obtained.

Utilizing radioactive diodrast, Winter[3] has been able to measure unilateral renal function without recourse to instrumentation. This technique may eventually have considerable importance as a screening test.

Chemical determination of catechol amines[4] in the urine offers the most direct way to diagnosing the presence of a .pheochromocytoma. The latter may be suspected in a young hypertensive who shows a significant drop in blood pressure when standing, or who has an elevated fasting blood sugar, elevated basal metabolic rate and gives a history of excessive perspiration. It should also be emphasized that false positive Regitine tests do occur and if possible should be confirmed with either a Benzodioxane or a urine catechol amine determination. Previous administration of antihypertensive drugs interfere with Regitine tests.

The rare case of primary aldosteronism[5] can be suspected when serum potassium is low, serum sodium high or normal, serum chloride low, associated with a high carbon dioxide combining power and persistently alkaline urine.

Once the etiological basis of the hypertension has been determined, an evaluation of its severity has to be made. Frant's[6] studies indicate that the higher the diastolic level of pressure, the worse is the prognosis but severity cannot be based merely on blood pressure levels since in any hypertensive patient, regardless of blood pressure level coronary thrombosis, cerebral vascular accidents, and acute left ventricular failure can occur without warning. At times, the first inkling that hypertension is present is the development of a cardiac or cerebral complication. There also are hypertensive patients who remain asymptomatic for many years despite markedly elevated blood pressures.[7-8]. Clinical symptoms mainly are determined by the presence and location of the arteriosclerotic process. The etiology of the latter is still speculative but probably is accelerated by the associated hypertension. It has been traditional to determine the severity of arteriolar disease by ophthalmoscopic examination of the fundus. At times, a lack of correlation in the retinal arteriolar findings with the important clinical findings does occur which tends to confuse the clinician. However, funduscopic findings as described in the classification by Wagener and Keith[9] serves as a useful indicator of the severity of the arteriolar sclerosis throughout the body. Thus evaluation cannot be reduced to simple terms, but must include a consideration of the level of diastolic pressure, evidences of vascular damage in the eye, heart, kidneys and brain and progressiveness of clinical symptoms.

TABLE I
CLASSIFICATION OF HYPERTENSION*

I. ARTERIAL HYPERTENSION (Blood pressure 150/90 or greater)
  A. ESSENTIAL HYPERTENSION
  B. RENAL
    (1) Nephritides
      (a) glomerulonephritis
      (b) pyelonephritis
      (c) gouty
      (d) toxic, due to lead intoxication
      (e) radiation nephritis
      (f) diabetic glomerulosclerosis
    (2) Diffuse Collagen Disease
      (a) Disseminated lupus erythematosus
      (b) Periarteritis nodosa
      (c) Scleroderma
    (3) Congenital Polycystic Kidney Disease
    (4) Nephrocalcinosis
    (5) Amyloid Disease
    (6) Obstructive Uropathy
    (7) Unilateral Kidney Disease
      (a) Inflammatory, embolic, or atherosclerotic obstruction of renal artery
      (b) Pyelonephritis
      (c) Tumor
      (d) Obstructive Uropathy
      (e) Perinephritis
    (8) Hypertension Due Toxemias of Pregnancy (May not be renal in origin)
  C. HORMONAL
    (1) Pheochromocytoma
    (2) Primary aldosteronism
    (3) Cushing's syndrome
    (4) Adreno-genital syndrome
  D. NEUROGENIC
    (1) Brain
      (a) Tumor
      (b) Concussion
      (c) Bulbar Poliomyelitis
      (d) Encephalitis
      (e) Meningitis
      (f) Diencephalic syndrome
  E. VASCULAR
    (1) Coarctation of the Aorta
II. SYSTOLIC HYPERTENTION (Increased Systolic Pressure Only)
  A. Due to Increased Cardiac Output
    (1) Complete Heart Block
    (2) Aortic Insufficiency
    (3) Patent Ductus Arteriosus
    (4) Hyperthyroidism
    (5) Arteriovenous Fistula
    (6) Severe Anemia
    (7) Paget's Disease
  B. Due to Decreased Elasticity of the Aorta
    (1) Arteriosclerosis of the Aorta
    (2) Coarctation of the Aorta

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*Actually the etiology of hypertension is unknown but a classification based on the main organ system involved in association with hypertension is of clinical value.

Selection Of Cases For Antihypertensive Drug Therapy

In the selection of patients for drug therapy, certain basic principles must be understood. It is generally agreed that a sustained reduction in diastolic pressure results in reduced cardiac work with subsequent improvement in cardiac function. Cardiac compensation is more easily maintained. Heart size may return to normal. A left ventricular hypertrophy pattern in the electrocardiogram may disappear. Improvement in retinal findings and renal function may occur. The rapid downhill course of "accelerated" or malignant hypertension can be controlled. By reducing blood pressure, the progressiveness of the arteriolar sclerosis may be reduced. However, rapid reduction in blood pressure also results in reduced blood flow, and increases the tendency to thrombosis, thus uremia, cerebral and coronary thrombosis can occur. Side-reactions as postural hypotension, constipation, unpleasant blurred vision, fatigue, impotence, dryness of mouth, nasal congestion, bizarre dreams, and depression, may accompany drug therapy. Even in the most enthusiastic hands, success in dropping blood pressure significantly with drug therapy is not predictable and may not occur in all treated patients. However, in well controlled series, the hazards are minimal and not serious. Thus the physician now has available a remarkable variety of drugs, all differing in their modes of action that have the capacity of reducing blood pressure effectively in a significant number of patients.

While is is not easy to place hypertensive patients in neat, rigid groupings nevertheless there are several groups about which there is no controversy concerning the advisability of administering hypotensive drugs.

Certainly any patient with malignant or the "accelerated" phase of essential hypertension can benefit from antihypertensive drug therapy. Schroeder[10] has demonstrated marked benefits with therapy in this group.

Patients whose diastolic pressures are 110 mm of mercury or over and who have shown evidences of progressiveness after physical and laboratory examinations should receive specific drug therapy.

Patients with diastolic pressures between 100 and 110 mm of mercury are treated only if they exhibit clinical progressiveness and complications due to hypertensive cardiovascular diesase. Evaluation of treatment in the milder hypertensives is not yet available but it seems reasonable to conclude that if the diastolic pressure can be maintained at about normal or slightly elevated pressure levels there should be improved cardiac and renal function and possibly reduced progressiveness in the associated vascular disease.

Patients whose diastolic pressures are below 100 mm of mercury probably require no specific therapy. Meilman[11] also feels that patients, particularly elderly ones, whose hypertension has proven benign by its long duration and who show only a moderate degree of cardiac enlargement, probably require no intensive therapy. However, it should be pointed out, that although certain older hypertensives may have a normal life span individual selection within the group is difficult and prediction of prognosis is uncretain.

Acute hypertensive crises associated with encephalopathy, toxemias of pregnancy, acute nephritis, and cerebro-vascular accidents can also benefit from therapy. We now have available for parenteral use hypotensive drugs which are reasonably prompt in reducing blood pressure.

There are also some absolute contraindications to the use of some of the new antihypertensive drugs. Recent coronary or cerebral thrombosis, and advanced renal insufficiency contraindicate vigorous, immediate therapy particularly with the ganglionic blocking agents. Obviously, an unintelligent and uncooperative patient makes this type of therapy also hazardous.

Hypotensive Drug Therapy

If it has been determined that a patient is to receive hypotensive drug therapy, the physician has to decide which particular drug to use. Criteria for this selection are controversial and only a trial can determine the effectiveness of any particular drug in any patient. It seems to be generally agreed that the use of a Rawolfia preparation is the initial drug of choice. It is unusually mild as regards toxicity, relieves anxiety, slows the pulse rate and appears to be synergistic with all other hypoten-

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LABORATORY STUDIES

I. ROUTINE
    A. Blood pressure determination both arms, sitting, lying, and standing
    B. Palpation femoral artery pulsations. Blood pressure legs
    C. Complete blood count
    D. Urinalysis, chemical and microscopic. Dilution and concentration test
    E. Blood chemical studies (1) Urea Nitrogen (2) Fasting Blood sugar (3) Serum Sodium and Potassium (4) Cholesterol
    F. X-ray to determine cardiac contour and size
    G. Electrocardiogram
    H. Funduscopic examination

II. Renal
    A. Intravenous and possibly retrograde pyelography
    B. Urine culture
    C. Blood chemical studies (1) Uric Acid (2) Calcium (3) Phosphorus (4) Alkaline and Acid Phosphatases (5) Total Proteins with Albumin and Globulin Ratio
    D. L-E cell preparation
    E. Congo red test
    F. Skin, muscle, gum biopsy
    G. Renal biopsy
    H. Excretion of sodium and water of each kidney. (Howard Test)
    I. Aortogram with visualization of renal arteries
    J. Radioactive diodrast renogram

III. Hormonal
    A. Regitine test
    B. Catechol amine determination in blood and urine
    C. 17-Ketosteroid, II-oxysteroid, 17 hydroxycorticoid excretion
    D. Aldosterone excretion
    E. Perirenal air insufflation
    F. Serum sodium, potassium, chloride, carbon dioxide content and serum ph
    G. Protein bound iodine

IV. NEUROGENIC
    A. Skull x-ray, possible ventriculogram and/or cerebral arteriography
    B. Spinal fluid pressure and chemical studies
    C. Electroencephalogram

sive drugs. Its mode of action is presumably at the hypothalamic area where it inhibits sympathetic activity. Its effectiveness in reducing blood pressure is greatest in the mild, labile hypertensive. There are a wide variety of commercial Rawolfia preparations available. The crude root, standardized alkaloidal extracts and purified alkaloid have essentially similar pharmacologic properties as regards their hypotensive effectiveness. Reserpine, the pure alkaloid, has an average dose of 0.5 milligrams daily.

Satisfactory blood pressure reduction through the use of Rawolfia preparations occurs in only a small proportion of patients and the selection of additional medication poses a therapeutic problem. Either a veratrum preparation or apresoline can be tried. The former reduces blood pressure by a series of reflexes mediated via the chemoreceptors, and baroceptors located in the carotid sinus, carotid body and myocardium. The narrow range between toxic and therapeutic doses and its mild hypotensive effects limits its usefulness. Apresoline, a true renal vasodilator, reduces blood pressure presumably by reducing peripheral resistance as a result of centrally induced peripheral vasodilation. It also increases cardiac rate and cardiac output. The latter qualities at times have resulted in an aggravation of an anginal syndrome and may make control of congestive heart failure hazardous. If total daily dosage is kept below 400 mgm. daily, serious toxicity is rare. Above this dosage a "lupus" like syndrome may occur in about 10% of treated patients. Apresoline has proven itself an effective hypotensive agent in mild to moderately severe hypertensive patients.

If drastic lowering of diastolic pressure is advisable, the use of the ganglionic blocking agents is indicated. Hexamethonium has been largely replaced by pentolinium tartrate (Ansolysem), chlorisondamine dimethochloride (Ecolid) and mecamylamine (Inversine). The principal effect of these drugs is believed to be a result of synapse blockade at both the sympathetic and parasympathetic ganglia. These agents vary in their absorbability and thus dosage and toxicity at times are unpredictable. For example, the absorption of Hexamethonium is 6%, Ansolysem, 22%, Ecolid, 22%. Inversine is believed to be totally absorbed and thus may be a more predictable agent. The effective dose of Inversine ranges from 5 to 25 mgm. daily, of Ansolysem, 60 to 500 mgm., of Ecolid, 25 to 200 mgm. of Hemamethonium 500 mgm. to 4 grams. The introduction of the ganglionic blocking agents should begin with very small oral doses and dosage increases should be determined by blood pressure responses in the upright position. It is preferable to record this pressure approximately two hours after the ingestion of medication. Initial dose of Inversine being 1.0 mgm. If no postural hypotension ensues two hours after administration, the dose should be doubled and given every 8 hours. Dosage then is increased by 2.5 mgm. every other day until the desired effect is obtained. Moyer[12] prefers dosages given at 7 AM, noon, 5 PM and 10 PM. The initial dose of Ansolysem is 10 mgm. The dose is increased by 20 mgm. slowly every other day until faintness in the upright position occurs. Three doses daily are given, generally after breakfast, in mid afternoon and at bedtime. Each dose need not be equal and study of the upright blood pressure responses at various times in the day indicate the desirability of making one dose larger than the other. The initial dose of Ecolid is 10 mgm. In view of its long duration of effectiveness Ecolid is repeated every 12 hours, generally being given after breakfast and supper. Dosage is increased 25 mgm. every other day until desired effect on pressure is obtained. Darvill[13] has administered in severe hypertensives as much as 60 mgm. per day before considering Ecolid ineffectual.

Acceptance of ganglionic blocking medication is narrowed by the wide variety of undesirable side effects. Severe constipation, at times associated with true ileus occurs. Cascara, prostigmine, neostigmine, or enemas are often required for adequate bowel evacuation. Neostigmine may render the synapse blockade less effectual and thus is used only when urgently required. Impotence may be a major problem. Discontinuing the medication for a day often corrects this complaint. Blurred vision, dryness of the mouth, urinary retention are generally not too serious. Severe postural hypotension may respond to recumbency, but at times neosynephrine administration is advisable.

Acute encephalopathy responds to intravenous veratrum or intramuscular reserpine administration. One can also use Inversine, Ansolysem, or Hexamethonium intravenously. The greatest caution should be exercised under these conditions since the drop in blood pressure may be precipitous and uncontrollable.

Surgery

The Peet or Smithwick type of sympathectomy is now reserved for the patient with malignant hypertension unresponsive to intensive hypotensive drug therapy. It may be recommended to patients with malignant hypertension or severe hypertensives who for various reasons do not care to subject themselves to the careful regimen required by drug therapy. In general surgical sympathectomy has been superseded by medical sympathectomy. If surgical sympathectomy is unsuccessful in reducing blood pressure, drug therapy then may become effective.

Diet

Low sodium diets (200 mgm.) are effective in reducing blood pressure. These are unpalatable and are acceptable for only short periods of time. With the use of hypotensive drugs, strict adherence to severe sodium restriction is not essential.

Low fat, low cholesterol diets have been recommended to control atherosclerosis. These are still controversial since the etiology of atherosclerosis is unknown. If the blood cholesterol level is above normal then the use of this type of diet is probably advisable. Further studies regarding the relationship between diet and atherosclerosis will be required before being able to definitely establish its effectiveness.

Addendum:

Since the completion of this resume, Wilkins[*] has introduced the use of Diuril as a hypotensive agent. While its effectiveness may be related to its ability to augment sodium excretion, it has been demonstrated that in some patients hypotensive effects may occur without reduction in serum sodium or body weight. Diuril also makes the ganglionic blocking agents more effective presumably because it increases sodium excretion. The starting dose of Diuril is 125 mgm three times daily and maximal dose, 500 mgm three times daily.

MAURICE R. CHASSIN, M.D., F.A.C.P.
Maspeth, New York

REFERENCES

1 Masters, A. M., Goldstein, I. and Walters, M. B.: "New and Old Definitions of Normal Blood Pressure: Clinical Significance of New Established Limits," *Bull. N. Y. Acad. of Med.*, 27:452, 1951.

2 Howard, J. E., Conner, T. B. and Thomas, W. C.: "Function Test for Detection of Hypertension Produced by One Kidney: Preliminary Studies," *Tr. A. Am. Physicians*, 69:291, 1956.

3 Winter, C. C.: "New Renal Function Test: The Radioactive Diodrast Renogram," *J. Urol.*, 76:182, 1956.

4 Goldenberg, M., Serlin, I., Edwards, T. and Rapport, M. M.: "Chemical Screening Methods for the Diagnosis of Phenochromocytoma. 1. Nor-Epinephrine and Epinephrine in Human Urine," *Am. J. Med.*, 16:310, 1954.

5 Conn, J. W. and Louis, L. H.: "Primary Aldosteronism: A New Clinical Entity," *Ann. Int. Med.*, 44:1, 1956.

6 Frant, R. and Groen, J.: "Prognosis of Vascular Hypertension," *Arch. Int. Med.*, 85: 727, 1950.

7 Burgess, A. M.: "Excessive Hypertension of Long Duration," *New England J. Med.*, 239:75, 1948.

8 Bechgaard, P.: "Arterial Hypertension: Follow-up of 1,000 Hypertonics," *Acta Med. Scandinav. Supp.*, 172:3, 1946.

9 Wagener, H. P. and Keith, N. W.: "Diffuse Arteriolar Disease with Hypertension and Associated Retinal Lesions," *Med.*, 18:317, 1939.

10 Schroeder, H. A. and Perry, H. M.: "The Treatment of Hypertension with Modern Drugs," *Circulation*, 13:98, 1946.

11 Meilman, E.: "Management of Hypertensive Cardiovascular Disease," *Circulation*, 13:596, 1956.

12 Moyer, J. H. et al: "Drug Therapy (Mecamylamine) of Hypertension," *Arch. Int. Med.*, 98:187, 1956.

13 Darvill, F. T. and Bakke, J. L.: "Chlorisodamine (Ecolid) Chloride in Medical Treatment of Severe Hypertension," *J.A.M.A.*, 163:429, 1957.

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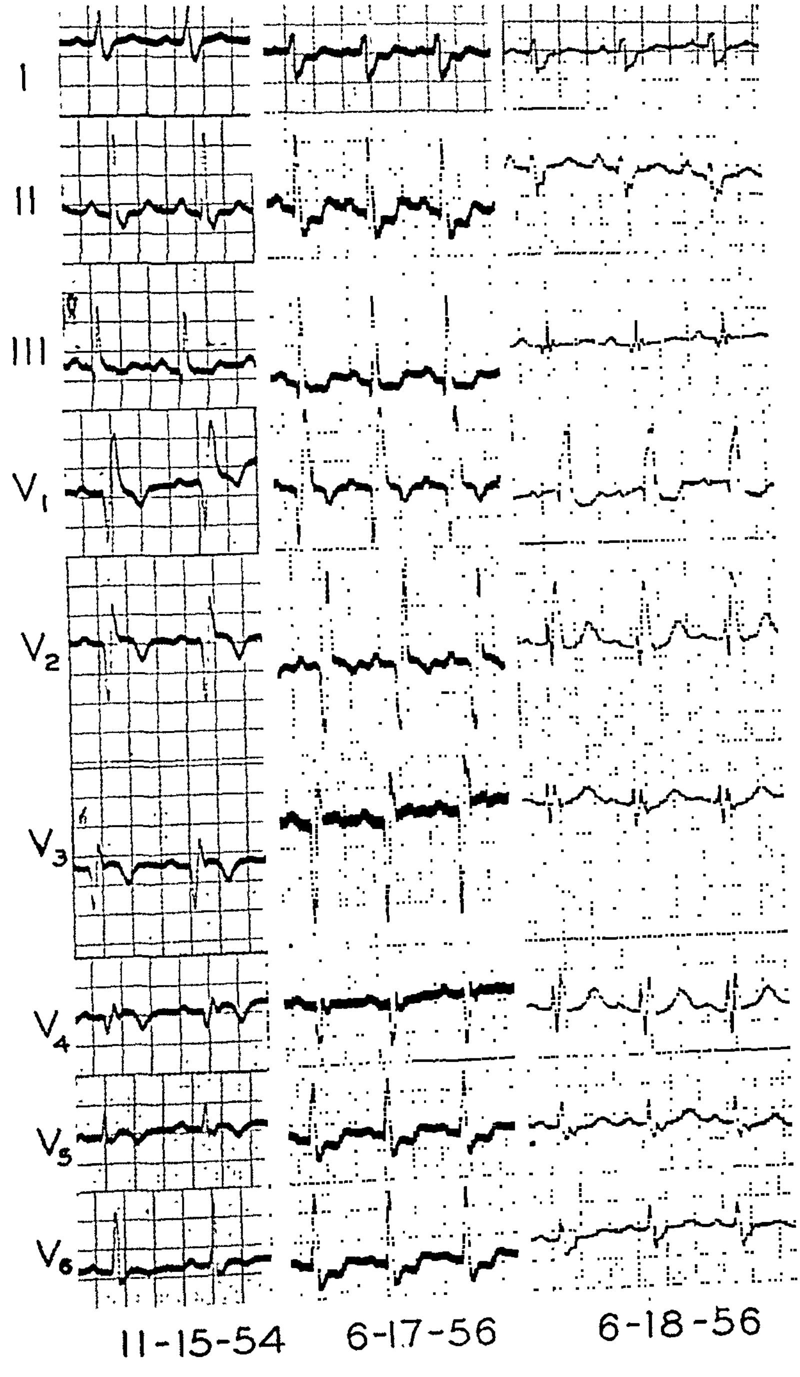
[*] Wilkins, R. W.: "New Drugs for Hypertension with Special Reference to Chlorathrazide," *New England J. Med.*, 257:1026, 1957.

THE ELECTROCARDIOGRAM OF THE MONTH

The authors would be pleased to receive comment and controversy from readers in relation to explanations offered.

This 67 year old man was hospitalized for three weeks in 1949 because of a "blood clot in the heart." In April 1954 he began having episodes of substernal pain radiating into his neck which were relieved by nitroglycerin. Electrocardiogams recorded in 1954 and 1955 were similar and one of these is shown below (November 15, 1954). Physical examination on admission to the hospital revealed



no abnormalities. An electrocardiogram made while he was having pain is also shown above (June 17, 1956). His pain was relieved by parenteral Demerol and another electrocardiogram was made on the following day.

Interpretation

The electrocardiogram made on November 15, 1954 shows right bundle branch block and an old anteroseptal myocardial infarction. The tracing made during an episode of chest pain on June 17, 1956 shows depression of the ST segment in leads I, II, III, and V5 and V6 and elevation of the ST segment in leads V2 and V3. These changes are indicative of posterior wall injury. The following day the injury shifts are no longer present. There is, however, a decrease in the height of the R waves in leads II and III and the large deep Q waves previously seen in leads V2, V3, and V4 are now preceded by R waves. Multiple precordial leads were made at various levels on June 18, 1956 to assure that the QRS changes seen were not due to a different placement of the chest electrodes.

The development of a posterior infarct in this patient resulted in an electrocardiogram which was not remarkable except for the presence of RBBB. If previous tracings were not available neither the fresh posterior infarction nor the old anterior infarction might have been suspected. The only suggestive feature seen in the tracing of June 18, 1956 is the large upright T wave in lead V2. The development of RBBB with an increase in the size of the R and/or R′ waves in leads over the right anterior chest usually results in a proportional decrease in the size of the T wave in these leads. Thus the large T wave in lead V2 is suggestive although not pathognomonic of posterior ischemia.

MANUEL GARDBERG, M.D. and IRVING L. ROSEN, M.D.*
New Orleans, Louisiana

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*From the Cardiac Research Laboratory, Touro Infirmary and the Department of Medicine, Louisiana State University Medical School.

CASE REPORT SECTION

Coronary Embolism and Acute Myocardial Infarction Secondary to Rheumatic Heart Disease

MURRAY S. HOFFMAN, M.D., JOHN FORREST, M.D. and E. LEE GARLETT, M.D.
Denver, Colorado

Rheumatic heart disease is not frequently considered a predisposing factor in the genesis of acute myocardial infarction. Coronary artery embolism is a diagnosis that is frequently not considered during life and is easily missed at the post mortem examination. The purpose of this article is to report and discuss a proved case of coronary artery embolism producing an acute fatal myocardial infarction in a patient with underlying rheumatic heart disease.

Case Report: A 64 year old white man entered the hospital for the first time on November 21, 1955. On the morning of admission, while in bed, he noted the sudden onset of crushing substernal pain which was extremely severe and radiated down the ulnar aspects of both arms. He felt quite weak and began to sweat profusely. At the same time, he noticed severe shortness of breath and appeared pale.

Past history was unremarkable. There were no known previous serious illnesses or operations. He had no known manifestation of rheumatic fever. System review and family history were non-contributory.

Physical examination at the time of admission to the hospital revealed a moderately obese man who was quite dyspneic and complained of severe chest pain. Temperature was 99° F., pulse 80, respiration 26 and blood presure 170/106 mm. of mercury. There was no cyanosis, clubbing or edema. Neck vessels were not unusually prominent. The lungs were clear. The point of maximum intensity of the apex beat was diffuse and extended to the fifth intercostal space in the left mid-clavicular line. A faint right ventricular thrust was present. A-2 was louder than P-2 and the second pulmonic sound was finely reduplicated. The mitral first sound was normal and no murmur was detected. Heart tones were of poor quality.

Laboratory examination revealed the following data: Urinalysis showed a trace of acetone but was otherwise negative. Hemoglobin was 17.7 gms. White blood cell count was 15,700 cells cu./mm. with 57 per cent segmented neutrophils, 23 per cent unsegmented neutrophils, 3 per cent eosinophils, 15 per cent lymphocytes and 2 per cent monocytes.

An electrocardiogram taken on admission (Fig. 1) demonstrated the classical findings of a massive, acute antero-lateral myocardial infarction. An electrocardiogram taken two days later was essentially unchanged except that the rate had increased to 115, and premature atrial contractions were much more frequent.

After admission to the hospital, he was placed on bed rest and given supplementary oxygen. Morphine sulfate grains one quarter was administered frequently, but failed to completely control the pain. Additional therapy included papaverine grains 3, 4 times a day and dicumarol 100 mg. on three successive days. During the first four hospital days, his condition remained critical and he frequently complained of chest pain. At 2:00 A.M. on the morning of the fifth hospital day, he became restless; his blood pressure fell to 80/30 mm. of mercury and his skin became cool and clammy. At 4:00 A.M., he had a slight convulsion and was essentially non-responsive thereafter. At 9:20 A.M. he expired.

At autopsy, the body weighed 98 Kg. and measured 170 cm. The pleural cavities contained 150 cc. of straw colored fluid bilaterally. The pericardial sac was lined by roughened membranes over which were several layers of fibrin. The parietal and visceral pericardium contained multiple petechiae. The heart weighed 530 gms., and the myocardium appeared soft and flabby. The left ventricle was dilated and the left

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From the Denver Rheumatic Fever Diagnostic Service, University of Colorado School of Medicine and the Department of Cardiology, National Jewish Hospital at Denver.

ventricular wall measured 1.5 cm. The right ventricular wall measured 0.5 cm. in thickness. The leaflets of the tricuspid and pulmonic valves were thin and delicate. The aortic cusps were minimally calcified, thickened and fused with one another. Over the free edges and the aortic surfaces were occasional calcified verrucous masses. Slight aortic stenosis was thought to be present. The mitral leaflets as well as the chordae tendineae were markedly thickened and fused. The mitral valve was definitely and significantly stenotic. There was dilatation of the right and left auricles, and the left auricular appendage was almost completely filled with a thrombus. The left coronary ostium was widely patent and appeared two to three time normal size. Both the circumflex and anterior descending branches of the left coronary artery were partially to completely occluded by embolic masses. The right coronary artery was hypoplastic. On section the myocardium of the anterior wall, septum, apex and adjacent sections of the posterior wall was grayish yellow and hemorrhagic in appearance. This was thought to represent an acute myocardial infarct.

The left lung weighed 330 gms. and the right 360 gms. The lungs were crepitant.

Microscopic examination of the heart revealed typical findings of an acute myocardial infarction approximately five days old. The wall of the left coronary artery was thin with minimal atheromatous changes. In the center of the vessel and completely occluding it was a solid fibrinous mass (Figure 2) consistent with the diagnosis of an embolus from the atrial appendage. The embolus appeared to be the same age on microscopic examination as the left atrial thrombus (Figure 3).

Discussion

The first case of coronary embolism was reported by Virchow[1] in 1856. In 1953 Cheng, Cahill, and Foley[2] collected a series of 54 proved cases. More recently individual cases have been described by Watts[3] and Flake.[4] Although there have been other reports, it is apparent that there have been relatively few documented cases of coronary embolization. Hamman[5] estimates the incidence of coronary embolism to be 1 to 2 per cent of all coronary occlusions.

Based on the reported cases, there are several sources of the embolic material. In order of frequency they are: (1) Bacterial vegetations on the mitral and aortic valves due to bacterial endocarditis (2) mural thrombi

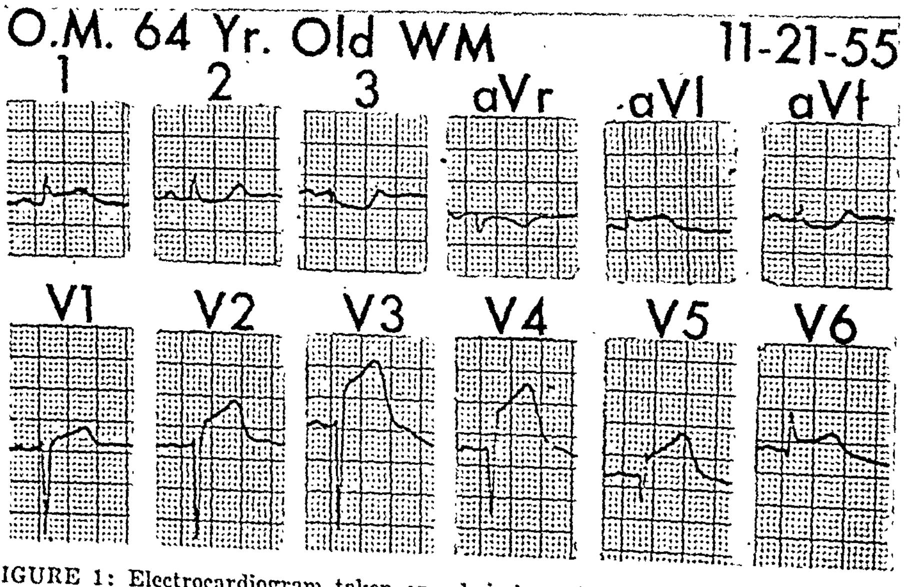

FIGURE 1: Electrocardiogram taken on admission. Tracing reveals typical findings of acute antero-lateral myocardial infarction.

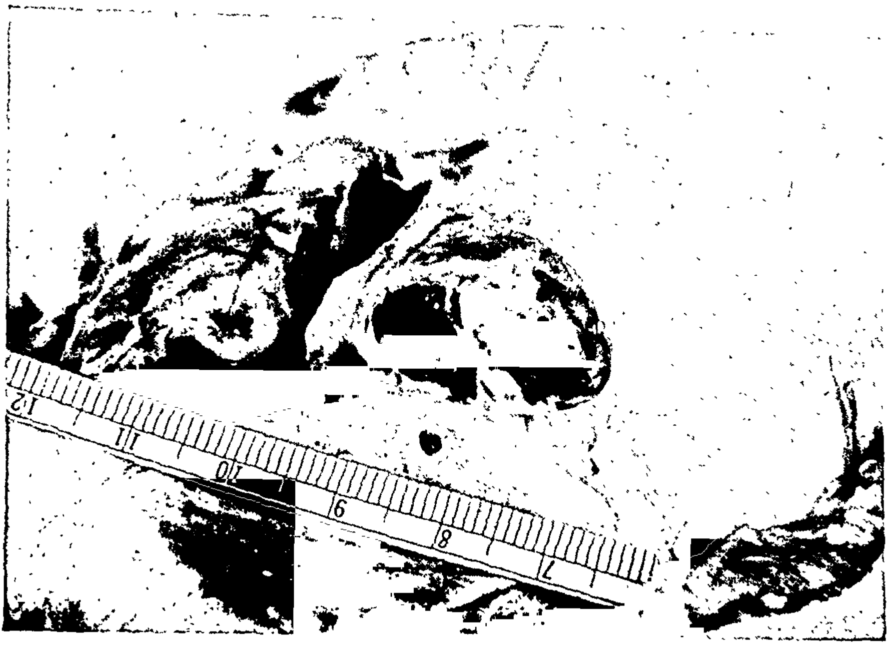

FIGURE 2: Thrombus in left atrial appendage. Below this is seen the intra-mural left coronary artery occluded by an embolus.

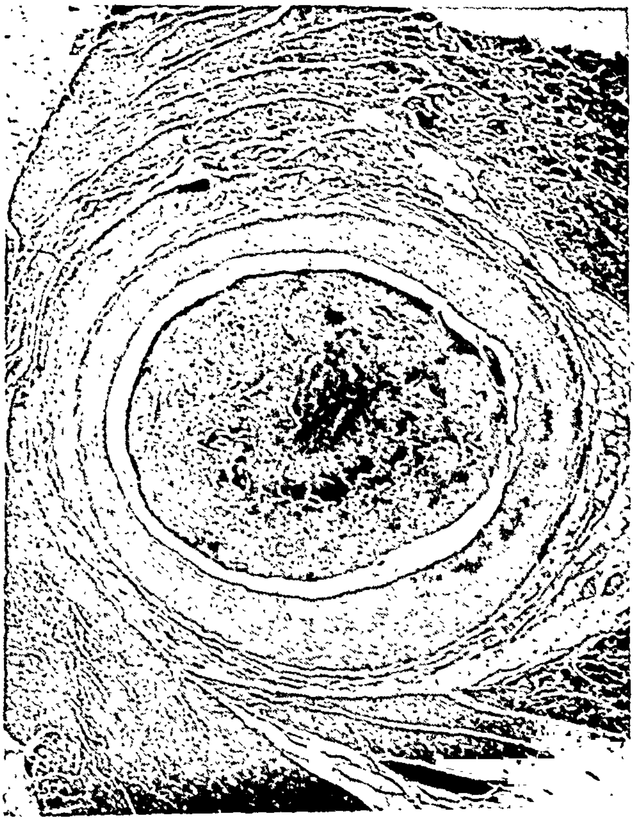

FIGURE 3: Left coronary artery. An embolus is clearly visualized with little or no attachment to the adjacent arterial wall. There are only minimal atherosclerotic changes in the wall of the artery itself.

on atherosclerotic or luetic lesions at the root of the aorta (3) intracardiac mural thrombi (4) thrombi in peripheral veins (paradoxical embolism) (5) thrombi in the pulmonary veins.

The difficulty in making an accurate ante mortem diagnosis of coronary embolism has been described by Hamman.[5] Certain features, however, stand out in the reported cases. Bacterial endocarditis is a well known source of emboli, and the sudden appearance of a myocardial infarction in a patient with bacterial endocarditis should make one suspicious.[6] Indeed, any cardiac patient or a patient with peripheral thrombophlebitis with sudden severe chest pain should alert the physician to the possibility of coronary embolism. Conditions that predispose to the formation of intracardiac thrombi, such as mitral stenosis, create the possibility of coronary emboli. Acute myocardial infarction in young individuals should also suggest the possibility of coronary embolism.

There are a number of post mortem findings in this case which help to definitely establish the pathological diagnosis of coronary embolism. The source of the embolus was clearly demonstrated in the left auricular appendage and the thrombus can be explained as being secondary to the rheumatic heart disease. In general, the arteriosclerotic changes in walls of the coronary arteries were minimal and were insufficient to explain the massive myocardial infarction on the basis of atherosclerosis.

Sections of the left coronary artery clearly showed this artery to have an intra-mural course. This anatomical variation was first described by Geiringer[7] who concluded that the incidence of atheromatous change in these intra-mural vessels was much less than is normally seen in extramural arteries. Although this conclusion has not been substantiated by Edwards,[8] certainly the left coronary artery in the present case showed minimal atheromatous changes. Another factor of importance in the present case is that the left coronary ostium was two to three times the normal size while the right coronary artery was hypoplastic thus resulting in a greater ease of embolization to the left coronary artery than would normally be present.

The diagnosis of rheumatic heart disease and coronary embolization probably could not have been made in this case prior to the patient's death, since there were none of the clinical criteria necessary for the ante-mortem diagnosis. Although the diagnosis of rheumatic heart disease with mitral stenosis was quite evident at autopsy, there was no suggestive history and no murmurs were detected. While the typical auscultatory findings may have been missed, this would seem to be unlikely, because of the repeated and frequent examinations of the patient. Mitral stenosis without murmurs does occur and has been described by Levine.[9] He attributes this phenomenon primarily to decreased blood flow across the stenotic valve which might occur in shock, congestive failure, atrial fibrillation, or marked dilatation of the heart. The typical auscultatory findings are made more difficult to hear by such factors as pulmonary emphysema, obesity, fluid in the chest cavity, and distant heart sounds. Dilatation of the heart and shock may well have been important factors in the present case.

REFERENCES

1 Virchow, R.: *Gesammel te Abhandlungan zur Wissenschoftlichen Medicinc*, Frankfurt, A. Meidinger Company, 1856.
2 Cheng, J. T. O., Cahill, W. J. and Foley, E. F.: "Coronary Embolism," *J.A.M.A.*, 153:211, 1953.
3 Watts, R. W.: "Coarctation of the Aorta Complicated by Acute Bacterial Endocarditis with Embolism of a Coronary Artery and Syphilitis Aortitis," *Am. Heart Jr.*, 43:111, 1952.
4 Flake, E. B. and Mathews, W. R.: "Coronary Embolism," *J. Louisiana M. Soc.*, 105:103, 1953.
5 Hamman, L.: "Coronary Embolism," *American Heart Jr.*, 21:401, 1941.
6 Brunson, J. G.: "Coronary Embolism in Bacterial Endocarditis," *Am. J. Path.*, 29:689, 1953.
7 Geiringer, E.: "The Relation of Mural Coronary Artery to Arteriosclerosis," *Am. Heart Jr.*, 41:359, 1951.
8 Edwards, J. C., Burnsides, C., Swarm, R. L. and Lansing, A. I.: "Arteriosclerosis in the Intramural and Extramural Portions of Coronary Arteries in Human Hearts," *Circulation*, 13:235, 1956.
9 Levine, S. A. and Love, D. E.: "Mitral Stenosis without Murmurs," *Cardiologia*, 21:599, 1952.

Effect of Lateral Recumbency on Pulmonary Function

ZOLTAN MANN, M.D., F.C.C.P.
Alexandria, Louisiana

It is the general belief that in the lateral recumbent position, which is a frequent position during bed rest, the lower chest, the one which is in contact with the mattress, expands less and consequently its function is diminished. Several authors[1-6] have investigated this function by means of clinical observations, radiographical and spirometric examinations but the result of these investigations and the interpretations of the findings were contradictory.

Adams and Pillsbury[1] believed that the excursion of the lower hemi-diaphragm had a greater respiratory efficiency. Webb, Foster and Gilbert[2] found the tidal movement of the lower hemi-diaphragm greater than that of the upper; however, after an interval of about an hour it equalized. Contrary to this finding, Pierson and Newell,[3] who made their investigations primarily in dogs, did not find the tidal ventilation to be equalized after a longer time.

Vaccarezza and his collaborators[4] found increased oxygen consumption through spirometric determination, greater complemental air, and increased vital capacity of the recumbent lung on a person who maintained the same position for two weeks; however, they supposed that the recumbent lung is in elastic repose.

Rothstein, Landis and Narodic[5] found spirometrically that oxygen consumption of the recumbent lung is increased. This finding was perplexing to them and they explained this increase as due to the larger capillary bed from relative congestion.

From the Veterans Administration Hospital.

Wade and Gibson[6] found that the diaphragmatic excursion, measured by a special device, showed a slightly greater excursion of the lower diaphragm. They believed, however, that this increased excursion is not sufficient to increase the respiratory function because the expansion of the lower part of the thoracic cage is reduced.

The purpose of this investigation is to demonstrate, by clinical observations substantiated by radiographic findings, that the function of the recumbent lung is increased and the function of the upper lung is decreased. Spirometric tests were not done since the results of such physiological studies have been considered and presented by others.[4-5]

Hypothesis, Method and Findings:

It was supposed that in lateral recumbent position the function of the upper lung is diminished because in this position the upper shoulder is caudad and the upper hip is cephalad and the arm usually rests on the chest wall. These factors exercise a splint-like action on the upper chest. The function of the lower lung is actually increased because the lower shoulder in this position is cephalad which pulls up the shoulder girdle and the hip is caudad. This permits maximum excursion of the ribs. This excursion is further facilitated by the fact that the patient is lying on two prominent bony structures—the hip and the shoulder. This position is illustrated in Figure 1. Mattresses exert some resistance against the lower chest but not enough to prevent the pulling action of the shoulder girdle where several secondary inspiratory muscles are attached. To substantiate this supposition by radiological findings, x-ray films in right lat-

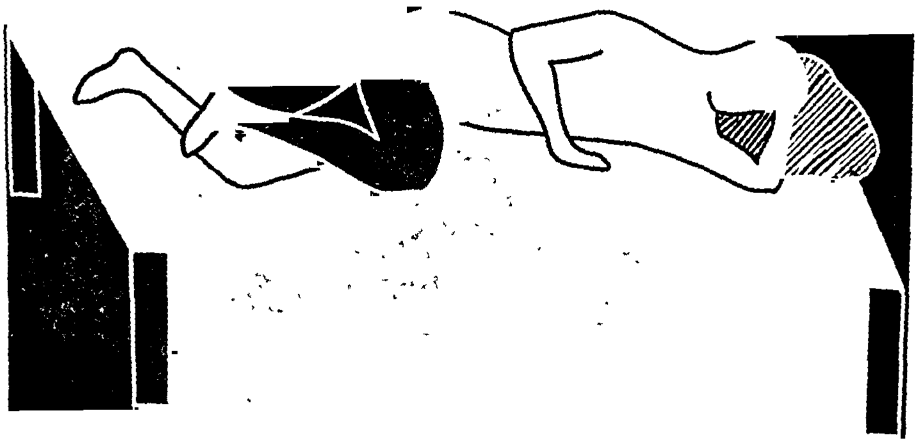

FIGURE 1: In lateral recumbent position, the upper shoulder is caudad; the upper hip is cephalad. The arm usually is leaning over the chest wall. The lower shoulder is cephalad and the lower hip is caudad. In this position the subject is lying on two prominent bony structures, that is, the hip and the shoulder.

eral decubitus were taken of a slender man (Figure 2), a slender woman, and a stout, short man in deep inspiration and full expiration. X-ray film was also taken of the stout, short man, in left lateral decubitus, for comparison. Roentgenogram in the upright position was also taken to show the physiological expansion of the chest and normal excursion of the diaphragm during the full phase of vital capacity (between full expiration and deep inspiration) (Figure 3).

All exposures were made from the standard six feet distance, the patient

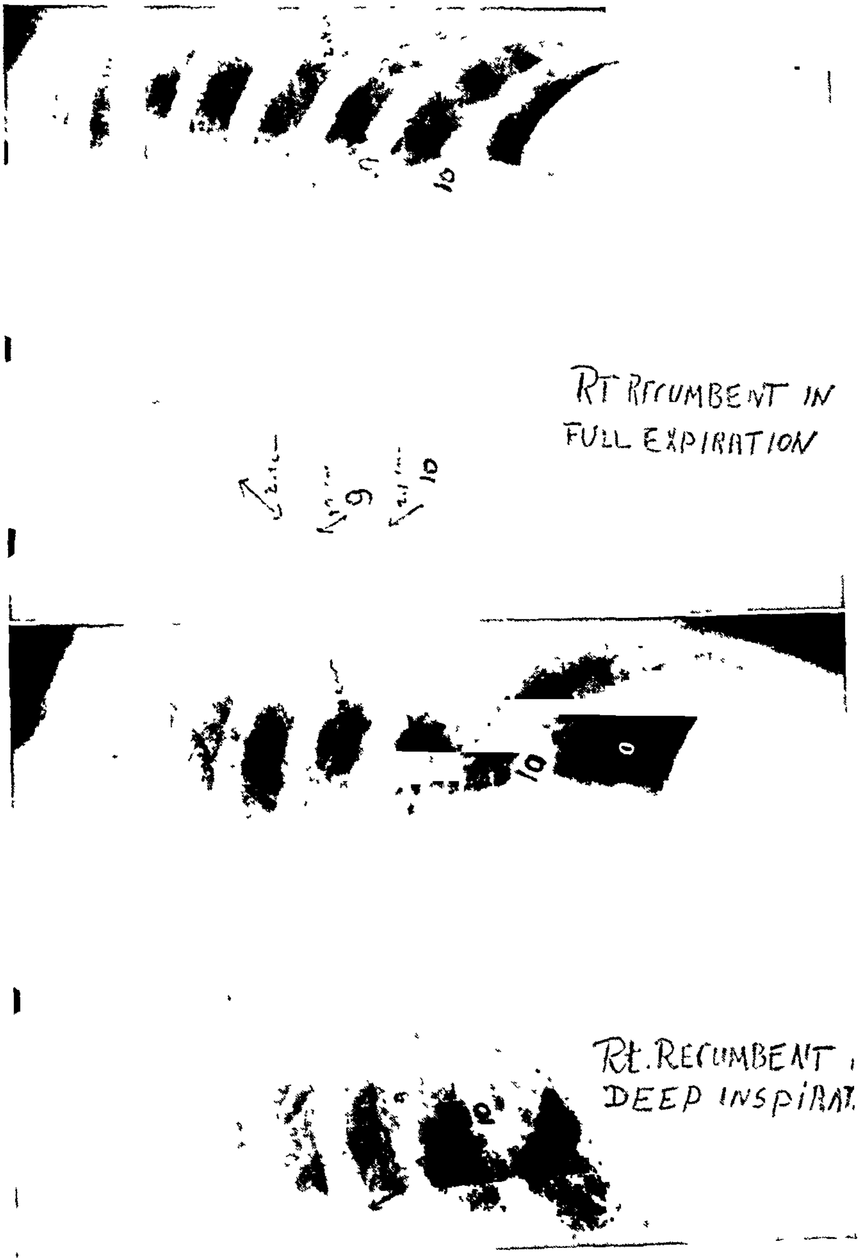
9
10
RT RECUMBENT IN FULL EXPIRATION
9
10
10
Rt. RECUMBENT, DEEP INSPIRAT.

FIGURE 2: Right lateral recumbent position in full expiration shows the right diaphragm at the level of the ninth posterior rib while the left is a little over the 11th. The same position in deep inspiration shows both diaphragms at the level of the 11th posterior rib. Note the marked airlessness of the right lung and the narrowing of the intercostal spaces in the expiration film.

lying in lateral recumbent position on a stretcher covered by a thin, one inch mattress.

It was found that in lateral recumbent position the hemi-diaphragm of the lower lung moved from the 11th posterior rib up to the ninth posterior rib between deep inspiration and full expiration, while the hemi-diaphragm of the upper lung hardly moved. In addition to this impressive finding, it could be seen that the under lung is markedly less aerated in expiration while the change in aeration of the upper lung is negligible. It can also be seen that in spite of the lower lung being in full expiration stage during deep expiration—as we can judge from the relative airlessness and the elevated diaphragm—the ribs of the lower thorax do not approximate correspondingly to the full expiration stage. This is the effect of the pulling action of the high shoulder girdle which does not permit the ribs to approximate and keeps the apical part of the lung in a constant anatomical expansion. Furthermore, it was evident that while the ribs over the under lung moved during respiration to a certain extent, in spite of the pull of the shoulder girdle, the ribs of the upper lung moved little or not at all. A marked shift of the mediastinum toward the recumbent side could be seen, especially on the plate of the young woman whose mediastinal structures are still elastic.

X-ray films of the short, stoutly built person show movement of the upper hemi-diaphragm. This moderate excursion of the upper chest wall is explained by the fact that the lower shoulder girdle and hip of this stout person are not so prominent; the lower chest leans over the mattress and consequently the upper shoulder and hip approach each other to a lesser extent permitting some excursion of the upper chest wall. The film of the slender woman showed the excursion of the lower hemi-diaphragm and the widening of the intercostal spaces even more pronounced. This is explained by taking into consideration that the hips of women are more prominent.

FIGURE 3: X-ray films taken in upright position of the same persons, show normal diaphragmatic excursion.

Comment

All of these findings, which are: the change of the intercostal spaces of the recumbent part of the chest wall, the change in aeration of under lung, the marked excursion of the lower hemi-diaphragm, the almost unchanging picture of the upper chest wall, lung field, and hemi-diaphragm, and the increased oxygen consumption of the under lung, clearly indicate that in the lateral recumbent position the function of the under chest wall, pleura, and lung increased, and of the upper is decreased.

REFERENCES

1 Adams, R. D. and Pillsbury, H. C.: "Position and Activities of Diaphragm as Affected by Change of Posture," *Arch. Int. Med.*, 29:245, 1922.

2 Webbs, C. B., Foster, A. N. and Gilbert, C. B.: "Postural Test for Pulmonary Tuberculosis," *J.A.M.A.*, 76:846, 1921.

3 Pierson P. H. and Newel, R. R.: "Pulmonary Rest by Posture," *Am. Rev. Tuberc.*, 33:1, 1936.

4 Vaccarezza, R. F., Lanari, A., Bence, A. E. and Lubourt, F.: "Influencia del Dec. Lat. Sobre El Reposo Pulmonar, Estudio Functional del Cada Uno Separado," *Ann. de Pat. Clin. Tuber.*, 3:254, 1941.

5 Rothstein, E., Landis, T. B. and Narodic, B. C.: "Bronchospirometry in Lateral Decubitus," *J. Thoracic Surg.*, 19:821, 1950.

6 Wade, O. D. and Gibson, I. C.: "Effect of Posture on Diaphragm Movement and Vital Cap. in Normal Subjects," *Thorax*, 6:103, 1951.

The Role of Medicine in World Peace

World peace is a hope that challenges the heart and mind. It is a desire that will be attained only by prodigious effort and by the will of man to understand the problems of his neighbor.

The theory is held by many that war is a biologic necessity and inevitable. The idea is not easily dislodged from the mind of man, for he has been indoctrinated with it through the centuries by advocates of the belief that "might makes right." War as a biologic necessity becomes absurd in the light of present-day scientific enlightenment, and the realization that to permit its occurrence is to court world destruction.

The struggle for world peace is a stupendous undertaking. It is an effort that requires the active participation of all members of society. The medical profession, because of its heritage and training in the alleviation of suffering, is especially destined to assume a place of leadership in this struggle. The well-informed physician appreciates that nations and customs change from time to time, but that the heart of man remains fundamentally the same. He is keenly aware of the importance of knowing the laws that govern the biologic organization of the individual and of human nature. Most important of all for the physician, his prerequisite of love of medicine must of necessity imply a love of humanity also.

History eloquently records that two of the dominant forces in the betterment of man have been religion and the healing art. That they should be so often associated in the mind of man as offering moral leadership is not surprising, for both are striving for the same purpose—the defense against evil. In ancient times disease, which is as old as life itself, was thought to be dealt with best by those chosen by the gods. With the dawn of reason and the casting aside of the fetters of superstition, knowledge became the criterion for the selection of the physician. But always a love of medicine has implied a love for humanity. These two qualities offer a basis for social leadership.

Statesmen have long recognized that physicians possess the qualifications essential in the production of leaders in the fight for peace, but deplore their reluctance to assume their proper place in world politics. They emphasize that physicians have the training and the close association to learn from the people their true hopes, aspirations, and degrees of fortitude, and that they are in a most favorable position to help direct the people's idealism into proper channels and implement it. Physicians are peculiarly qualified to judge the physical and, to a lesser extent, the mental capabilities of our leaders, and to warn the populace when disorders arise—disorders that so often may lead to tragedy and loss of human life and dignity. Medicine may indeed act as a catalyzing agent for better understanding among men, and a potent force against ignorance, which so often breeds evil.

Virchow, in 1849, forcefully described the responsibility that medicine must bear in order to assume its proper place in the life of man:

"Should medicine ever fulfill its greatest ends, it must enter into the larger political and social life of our time. It must indicate the barriers which obstruct the normal complications of the life cycle and remove them. Should this era come to pass medicine, whatever it may then be, will become the common good of all."[1] There are many in the medical profession who are fully aware of medicine's responsibility to humanity, are motivated by the high ideals of public service, and give gladly of their time and substance to bring such dreams to a full fruition. Others believe they are willing to join in this great crusade but never succeed in implementing such a belief with action. Finally, there are those who lack a sense of responsibility to humanity and are content to spend their lives in self-satisfied isolation, with no altruistic regard for their fellow-man.

Medicine, which is science in the making, can no longer enjoy the luxury of provincialism; for science, as Pasteur noted, knows no country. Although the voice of a single physician raised in behalf of humanity on the international scene may not always be heard, when augmented by the many voices of his associates it may have far-reaching effects. It is important that we in the medical profession not only combine our voices on matters of local concern, but also unite with our colleagues all over the world in a concerted effort for the betterment of mankind. At every opportunity we must join with other guilds and organizations, and those of other nations and races in the crusade for peace, if peace is ever to have birth.

One of the most potent and successful methods for promoting good will and understanding among physicians throughout the world is the international medical meeting. Such meetings afford a splendid opportunity for the exchange of ideas and information. They rapidly teach that physicians and other people, no matter what their race, creed, or origin, have many of the same hopes and dreams, and that many of the apparent differences are mere misunderstandings based on ignorance. How refreshing and stimulating it is to realize that good ideals and ideas can come from so many!

The American College of Chest Physicians has been a pioneer in the promotion of international medical meetings and has aided greatly in the dissemination of medical knowledge and the promotion of better understanding among men. The next international meeting of the American College of Chest Physicians is to be held in Tokyo, Japan, in September of this year. Not only does it promise to be highly educational and instructive, but also it affords a splendid opportunity to enjoy the famous hospitality of an oriental nation. It should do much to promote international understanding and a realization that to know is not to fear, for knowledge and truth conquer all.

REFERENCE

1 Virchow, R.: Preface to the Fourth Edition. In Garrison, F. H.: *History of Medicine.* Ed. 4, Philadelphia, W. B. Saunders Company, 1929, p. 6.

HERMAN J. MOERSCH, M.D., F.C.C.P.
Rochester, Minnesota

Section of Medicine, Mayo Clinic.

The President's Page

The annual reunion of College members and their families is drawing near and I am sure we are all looking forward to a most successful and enjoyable meeting in San Francisco. A glance at the scientific program as published in the April issue of *Diseases of the Chest*, would suffice, I believe, to induce all chest specialists to attend. Our program committee has, indeed, organized a most outstanding array of scientific sessions.

At this time of the year it is important that the members of all the College councils and committees give serious thought to their respective activities and especially to their plans for the future. All of the councils and committees of the College will hold their annual meetings at the Fairmont Hotel, San Francisco, on Thursday, June 19, when present activities and future programs for each committee will be discussed.

It will be of interest to all members of the College, I know, to learn that there will be three special events in San Francisco sponsored by councils of the College. The first will take place on Wednesday afternoon, June 18, and is sponsored by the Council on Undergraduate Medical Education. The subject under discussion at this Seminar will be "Undergraduate Teaching of Tuberculosis and Chest Diseases at the University of California School of Medicine," in which members of the staff at the University will present their teaching methods. Questions and discussion from the floor will be welcome. College members concerned with undergraduate teaching will undoubtedly be able to glean some valuable ideas from this session.

Two special events will take place on Thursday afternoon, June 19. One will be an open forum of the Council on Research where reports from various committees will be presented. Except for one or two occasions, the meetings of the Council on Research have been closed sessions. However, the College membership has expressed great interest in hearing the reports of the committees which serve under the Research Council and it was decreed by the Board of Regents to open the session to all College members.

The other special event scheduled for Thursday afternoon, which we are certain will interest a great many members, is the Open Forum sponsored by our Council on Hospitals. This year the subject of the forum is "Have We Exhausted Our Case-Finding in Chest Disease?" A number of experts in this field will present their views as they relate to communities, hospitals, schools and penal and mental institutions. We are therefore of the opinion that an open discussion on this timely topic could be of great value. I hope you will find it so and that you will contribute to the discussion or ask questions which will bring out the pertinent points.

Following are a few of the highlights of the scientific assembly that you will not want to miss. The "Panel on the Jet Age and Chest Medicine" will be presented on Thursday night, June 19. The Fireside Conferences, Friday night, June 20, will offer twenty-eight simultaneous conferences covering almost every conceivable subject in chest disease. Each table will be manned by two or more experts and refreshments will be served to liven the discussion. There will be a selection of eighteen round table luncheon discussions presented on Friday, Saturday and Sunday, June 20-21-22. These luncheons are always sold out in advance of the meeting and I would suggest that you reserve places at the luncheons of your choice at once.

The Committee on Motion Pictures of the College, under the chairmanship of Dr. Paul H. Holinger of Chicago, has organized a splendid program of motion pictures on chest disease to be presented in San Francisco. I would like to call your attention to the new list of approved motion pictures compiled by the committee and published in this issue of the journal. Reprints of this list may be obtained upon request. It will be a pleasure to see you in San Francisco.

Burgess L. Gordon

College Chapter News

ILLINOIS CHAPTER

The 19th annual meeting of the Illinois Chapter will be held at the Hotel Sherman, Chicago, on May 22, in conjunction with the meeting of the state medical association. The following program will be presented:

8:30 a.m. Registration
9:00 a.m. Herman C. Rogers, Mt. Vernon, President, Illinois Chapter, presiding
"Bronchial Asthma Fifty Years Ago and Today"
Max Samter, Chicago
"Treatment of Hypertension"
Sibley W. Hoobler, Ann Arbor, Michigan
"Etiologic Factors in the Production of Lung Cancer"
Wilhelm C. Hueper, Bethesda, Maryland
12:00 noon Luncheon and business meeting

NEW YORK STATE CHAPTER

The 18th annual dinner meeting of the New York State Chapter will be held at the Hotel Statler, New York City, May 15. Dr. Chevalier L. Jackson, Philadelphia, will present the Eighth Annual Howard Lilienthal Lecture entitled "The Bronchologist's Role in Modern Thoracic Surgery." On May 16, the following program will be presented in the Chest Disease Section of the Medical Society of the State of New York:

"Significance of Circulating Neoplastic Cells in Patients with Carcinoma of the Lung"
George E. Moore and Charles A. Ross, Buffalo
Discussion: Oscar Auerbach, East Orange, New Jersey and Herbert C. Maier, New York City
"Anatomic Studies of Coronary Arteries"
Allan Stranahan, Albany
Discussion: Simon Dack and Harry Gross, New York City
"Tracheal Fenestration as a New Method of Treatment of Advanced Emphysema"
Charles F. Blazsik, Edgar Mayer, Israel Rappaport, Edward E. Rockey and Samuel A. Thompson, New York City
Discussion: Ralph D. Alley, Albany and Alvan L. Barach, New York City

CUBAN CHAPTER

At the recent annual meeting of the Cuban Chapter in Havana, the following officers were elected:

President:	Luis P. Romaguera, Havana
Vice President:	Rogelio J. Barata, Havana
Secretary-Treasurer:	Rafael A. Gomez Zaldivar, Havana

JAPAN CHAPTER

The Japan Chapter held a meeting in Tokyo on February 11 when the following program was presented:

"Combined Chemical and Adrenocortex Hormone Therapy in Pulmonary Tuberculosis"
Jiro Gomi, Tokyo
"Tuberculosis Bronchiectasis"
Junjiro Okanishi, Tokyo
"Classification of Pulmonary Tuberculosis from the Standpoint of Chemotherapy"
Imazato Donomae, Osaka

Members, Japan Chapter, attending annual meeting February 11, 1958.

At the close of the scientific session, a business meeting was held at which the following officers were elected:

President:	Masanaka Terada, Tokyo
First Vice President:	Susumu Hibino, Nagoya
Second Vice President:	Harutaka Baba, Tokyo
Secretary-Treasurer:	Yoshio Hayashi, Tokyo

COLLEGE GROUP INSURANCE PROGRAM EXTENDED TO MEMBERS THROUGHOUT THE WORLD

The Joseph K. Dennis Company, Inc. of Chicago, Illinois, administrators of the ACCP Group Insurance Program, reports to the College that the ACCP Accidental Death—Dismemberment—and Loss of Sight Insurance Program has been extended to include all of our members around the world and the spouse of the member, so long as they are age 70 or under.

This recent improvement in the ACCP Group Insurance Program has been accomplished without any increase in premiums or decrease in benefits.

The ACCP Accidental Death—Dismemberment—and Loss of Sight Program provides six plans of coverage to choose from ranging from $25,000 to $200,000. The group premium is at the rate of $1.25 per $1,000.

The coverage afforded in this program is in effect 24 hours a day, 365 days a year, anywhere in the world, at work, at home, at play. Coverage is also provided for any mode of travel, so long as it is a licensed carrier and the insured is not a pilot or crew member of an aircraft.

Members outside the U. S. may apply for coverage under the ACCP Accidental Death—Dismemberment—and Loss of Sight Program; however, their premiums are payable at the American currency exchange rate and claims are paid on the same basis

This coverage provides maximum benefits at minimum group rates.

All inquiries concerning the ACCP Accidental Death—Dismemberment—and Loss of Sight Program may be directed to the ACCP Group Insurance Administration Office, the Joseph K. Dennis Company, Inc., Suite 1027, 175 West Jackson Boulevard, Chicago 4, Illinois.

College News Notes

Dr. A. Frederick Bloodworth, Gainesville, Georgia, recently addressed the Rotary Club of Gainesville on the scope of the specialty of diseases of the chest and the activities of the American College of Chest Physicians.

Dr. C. Walton Lillehei, Minneapolis, Minnesota, was recently named one of six recipients of the Purdue Frederick Medical Achievement Travel Award for outstanding medical and scientific activities.

Dr. Raffaele Paolucci de Valmaggiore, Rome, Italy, has been made President-Elect of the International College of Surgeons and will assume office in September, 1958. **Dr. Jorge A. Taiana**, Buenos Aires, Argentina, was elected a Vice-President of the organization.

The following Fellows of the College participated in a panel discussion on "The Management of the Patient with Cardiovascular Disease" at a meeting of the Westchester Heart Association and the Westchester County Medical Society on February 18 at Purchase, New York: **Drs. Houck E. Bolton, William Likoff**, Philadelphia, and **Charles K. Friedberg**, New York City.

Dr. William R. Barclay, Chicago, Illinois, and **Dr. Edward H. Robitzek**, Staten Island, New York, spoke at the meeting of the New York Tuberculosis and Health Association in New York City, April 30.

A medical-surgical building in Minneapolis will be named for **Dr. George E. Fahr**, Minneapolis, in honor of his contributions to the development of the electrocardiogram.

Drs. George E. Burch, New Orleans, Louisiana, and **Robert P. Glover**, Philadelphia, Pennsylvania, were lecturers at the Atlanta Graduate Medical Assembly held recently.

Brig. General Carl W. Tempel, Phoenixville, Pennsylvania, was the winner of the Stitt Award for meritorious achievement in the use of antibiotics in the treatment of tuberculosis. The award was presented by **Dr. Jerome J. Van Gasse** of the Chas. Pfizer Company.

Sir Harry Wunderly, Canberra, Australia, and **Dr. Robert T. Neubauer**, Ljubilijana, Yugoslavia, will participate in the NAPT Commonwealth Chest Conference to be held in London, July 1-4. They will speak on "The World Anti-tuberculosis Campaign. Is it Succeeding?"

During 1957, the following members of the College were guests of **Dr. Donato G. Alarcon** at the Sanatorio San Angel in Mexico City: **Jose Abello**, Madrid, Spain; **Andrew L. Banyai**, Milwaukee, Wisconsin; **Marvin S. Harris**, Los Angeles, California; **Meyer R. Lichtenstein**, Chicago, Illinois; **Leo G. Rigler**, Los Angeles, California; **Maurice S. Segal**, Boston, Massachusetts; **Harry Shubin**, Philadelphia, Pennsylvania; **Jose Valiente**, San Salvador, El Salvador; **Carlos Zurita**, Cordoba, Spain.

Dr. Edward A. Meyerding, St. Paul, Minnesota, has recently retired as Executive Secretary of the Minnesota Tuberculosis and Health Association after serving in this capacity for 34 years.

Dr. Clyde A. Watkins, Sanatorium, Mississippi, has been appointed Superintendent of the Mississippi State Sanatorium.

Drs. Carl Davis, Jr., Kenneth C. Johnston, Hiram T. Langston, and William M. Lees, Chicago, will serve on the Committee on Local Arrangements for the 1958 Congress of the American College of Surgeons to be held in Chicago, October 6-10. **Dr. John L. Keeley**, Chicago, will serve as Chairman of the Press Relations Committee. **Drs. Thomas G. Baffes**, Skokie and **Peter V. Moulder**, Chicago, will work with Dr. Keeley.

Dr. Nathaniel E. Reich, Brooklyn, New York, delivered several lectures at the Faculty of Medicine of Haiti, Port-au-Prince, at the invitation of the government of Haiti. While there, he met with **Dr. Francois Duvalier**, recently elected President of Haiti, and **Dr. Auguste Denize**, newly appointed Minister of Health in Haiti who is a Fellow of the College. The College Governor in Haiti is **Dr. Louis Roy**.

Committee on Motion Pictures
American College of Chest Physicians

The Committee on Motion Pictures of the American College of Chest Physicians is pleased to present the following list of films on diseases of the chest. A previous list was published by our committee in 1953. Since then, many new films have been prepared and this current list, we hope, will assist College members in undergraduate and postgraduate teaching of diseases of the chest. The films appropriate for use in undergraduate teaching have been marked with an asterisk. The titles have been divided into various categories for ease in selection of films on special subjects. Requests for the loan of films should be directed to the indicated source. Copies of the list, including an author index, will be sent upon request.

Paul H. Holinger, Chicago, Illinois, Chairman
Houck E. Bolton, Philadelphia, Pennsylvania
Eliot Corday, Beverly Hills, California
Francis E. Donoghue, Rochester, Minnesota
Karl P. Klassen, Columbus, Ohio

List of Approved Films

ANATOMY, PHYSIOLOGY, EMBRYOLOGY AND BACTERIOLOGY

*COCCIDIOIDOMYCOSIS, ITS EPIDEMIOLOGIC AND CLINICAL ASPECTS

Libero Ajello and Roger Egeberg, directed by Mr. Graham Heid, Public Health Service and Veterans Administration, Washington, D. C.

Distribution and habitat of the fungus, Coccidioides immitis, are described. The epidemiology and clinical manifestations are shown, employing x-rays, animation and photography of actual cases. The serology and laboratory procedures for isolating the organism are treated in some detail since these are the most certain methods of diagnosis. Sound, color, 19½ minutes (1956). Procurable from Audio-Visual Section, Communicable Disease Center, Public Health Service, Chamblee, Georgia.

*BRONCHOVASCULAR ANATOMY

William E. Bloomer, A. A. Liebow and M. R. Hales, New Haven, Connecticut

Makes use of vinylite injection-corrosion casts of human lungs obtained at autopsy, to demonstrate the segmental bronchovascular anatomy of the lung. Sound, color, 25 minutes (1953). Procurable from William E. Bloomer, M.D., 789 Howard Avenue, New Haven, Connecticut.

*MECHANICAL FACTORS GOVERNING EXPIRATORY OBSTRUCTION TO AIRFLOW

Howard G. Dayman, Chronic Disease Research Institute, University of Buffalo School of Medicine, Buffalo, N. Y.

Mechanical model of bronchi and lung animated to act as the bronchi in life show the collapsing effect of low lung tension, high rate of flow and obstruction. Dead lungs attached to cough machine show same phenomena, also living structures in movies of the fluoroscopic screen. These factors are reflected in specific pneumotachygraph patterns. Sound, color, 20 minutes (1954). Procurable from author, 993 Delaware Avenue, Buffalo 9, N. Y

*DYNAMICS OF THE TUBERCLE, IN VIVO OBSERVATIONS OF PATHOGENESIS AND EFFECTS OF CHEMOTHERAPY IN THE CLARK RABBIT EAR CHAMBER

Robert H. Ebert and William R. Barclay, University of Chicago School of Medicine, Chicago, Illinois; directed by David S. Ruhe, University of Kansas School of Medicine, Lawrence-Kansas City, Kansas; original research supported by grants from the U. S. Public Health Service; produced with support from Chas. Pfizer & Co., Brooklyn, N. Y.

This film is a demonstration of pathology of tuberculosis as observed in living tissue. A brief prologue compares the familiar fixed and stained histopathology of tuberculosis with the appearance of these lesions in live tissue (where changes in the blood vessels are the dominant phenomena). The rabbit ear chamber of A. E. Clark is explained by means of live views and animated drawings. A sheet of replacement connective tissue forms in the chamber from the surrounding tissue, and the characteristic appearance of the normal vessels, blood cells and connective tissue in the chamber is demonstrated. The film concludes with a rapid summary of the salient features of the dynamics of tubercle formation. Sound, color, 28 minutes (1956). Procurable from Chas. Pfizer & Co., Brooklyn, N. Y.

*ANTI-TUBERCULOSIS DRUGS IN THE MEDICAL AND SURGICAL TREATMENT OF TUBERCULOSIS

H. Corwin Hinshaw and Albert C. Daniels, San Francisco, California

The film deals with benefits from and the limitations of the modern anti-tuberculosis drugs, such as PAS, streptomycin, dihydrostreptomycin and nydrazid. Sound, color, 28 minutes (1953). Procurable from E. R. Squibb & Sons, 745 Fifth Avenue, New York, N. Y.

*Asterisk indicates film appropriate for undergraduate teaching.

*DEVELOPMENT OF THE AORTIC ARCH

George H. Humphreys II, Columbia-Presbyterian Medical Center, New York, N. Y.

Beginning with the gill-arch apparatus of water-breathing vertebrates, the film shows the changes which occur in air-breathing mammals, making possible their efficient *respiratory mechanism*. In *this evolutional* process, the development and involution of the primitive arches are carefully documented, up to the point, about the eighth week after ovulation, where the definitive arrangement of the great vessels has become established. With closure of the ductus arteriosus as respiration begins at term, the final, complex, asymetrical pattern of the human aortic arch is established. Sound, color, 14 minutes (1956). Procurable from E. R. Squibb & Sons, 745 Fifth Avenue, New York, N. Y.

*ANOMALIES OF THE AORTIC ARCH

George H. Humphreys II, Columbia-Presbyterian Medical Center, New York, N. Y.

This film is best used as a sequel to its companion, *Development of the Aortic Arch*, which sets the stage, so to speak, for the presentation of the common deviations from the normal which are depicted here. With an understanding of the probable course of events resulting in situations with which the surgeon may be confronted, he should be better able to make accurate diagnosis and evaluate conditions where the surgical intervention will be advisable. Sound, color, 30 minutes (1956). Procurable from E. R. Squibb & Sons, 745 Fifth Avenue, New York, N. Y.

*DEVELOPMENT OF THE HEART

George H. Humphreys II, Columbia-Presbyterian Medical Center, New York, N. Y.

This subject is covered here entirely in animation. Normal development is depicted in detail, and from several aspects, in whole as well as in parts, from the 3rd to the 11th week (*ovulation age*) *after* which changes are those of size only. Sound, color, 35 minutes (1958). Procurable from E. R. Squibb & Sons, 745 Fifth Avenue, New York, N. Y.

*THE BRONCHOPULMONARY SEGMENTS

Chevalier L. Jackson, John F. Huber and Charles M. Norris, Temple University School of Medicine and Hospital, Philadelphia, Pennsylvania

The film demonstrates that by inflation of fresh lung specimens and by means of dye injection, the anatomist can delimit individual segments, which he further identifies by dissection. Embryologically, each of the segments is represented by a bronchial bud. Histologic sections provide additional evidence that the segments are discrete entities. Sound, color, 30 minutes (1955). Also Available with French, German and Spanish sound tracks. Procurable from Chas. Pfizer & Co., 630 Flushing Avenue, Brooklyn 6, N. Y. and from the American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

*ACTION OF THE HUMAN HEART VALVES

Karl P. Klassen and C. V. Meckstroth, Ohio State University Health Center, Columbus, Ohio

Film shows the function of normal and abnormal heart valves under simulated physiological conditions. Correction of valvular dysfunction by surgery illustrated. Sound, color, 20 minutes (1956). Procurable from author, American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois, or from American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

*PRINCIPLES OF RESPIRATORY MECHANICS

Jere Mead, E. P. Radford, Jr., M. B. McIlroy, B. G. Ferris, Jr. and J. L. Whittenberger, Department of Physiology, Harvard Medical School, Boston, Massachusetts

Sound, color, 22 minutes (1955). Procurable from American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

*BCG VACCINATION AGAINST TUBERCULOSIS

National Tuberculosis Association, New York, N. Y., and Research Foundation, Chicago, Illinois

A physician explains the approved role of BCG vaccination in a complete tuberculosis control program and reviews the recommendations of the American Trudeau Society for the use of BCG vaccine. This physician presents the results of carefully controlled studies in the United States and some results from elsewhere throughout the world. The film, by actual demonstration, describes the administering of the tuberculin test and its reading. In an actual BCG vaccination he shows how freeze-dried BCG is prepared for use, and *demonstrates the multiple* puncture disc method of vaccination. Sound, color, 20 minutes (1954). Procurable from Research Foundation, 70 West Hubbard Street, Chicago 10, Illinois.

*RECORDING OXIMETERS AND THEIR APPLICATIONS

John F. Perkins, Jr. and William E. Adams, University of Chicago School of Medicine, Chicago, Illinois

The film begins with a picture of a Van Slyke apparatus during an analysis of blood for oxygen. The narrator makes the point that, in spite of the accuracy of the apparatus, continuous data regarding blood-oxygen content are not provided. The principles of oximeters are then briefly reviewed by means of a photoelectric exposure meter and transparent containers containing red and blue dyes to simulate oxygenated and reduced blood. Oximeter earpieces are shown, and various types of recording oximeters are demonstrated in use during teaching of respiratory physiology during various tests of pulmonary function, during an operation for valvulotomy, during an operation for pulmonic stenosis with atrial septal defect, and during post-operative oxygen therapy. Sound, color, 15 minutes (1953). Procurable from American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

*CONGENITAL MALFORMATIONS OF THE HEART (PART I: DEVELOPMENT OF THE NORMAL HEART)

Robert F. Rushmer and Richard J. Blandau, University of Washington, Seattle Washington

Actual development of the heart of a chick embryo. Animated drawings show the development and closure of the cardiac septa and the spiral septum. Sound, color, 15 minutes (1952). Procurable from The Film Center, University of Washington, Seattle 5, Washington, and from the American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

*CONGENITAL MALFORMATIONS OF THE HEART (PART II: ACYANOTIC CONGENITAL HEART DISEASE)

Robert F. Rushmer, University of Washington, Seattle, Washington

Instances of a number of congenital lesions of the heart and great vessels, grouping them under a single clinical yardstick of absence of cyanosis and under the physiological criterion of anomalies where blood flow from left heart to right heart is paramount. Sound, color, 14 minutes (1952). Procurable from The Film Center, University of Washington, Seattle 5, Washington, and from the American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

*CONGENITAL MALFORMATIONS OF THE HEART (PART III: CYANOTIC CONGENITAL HEART DISEASE)

Robert F. Rushmer, University of Washington, Seattle, Washington

Cyanosis in congenital heart disease, roles of (a) diminished blood through the lungs, and (b) shunting of venous blood into the systemic circulation. Includes tricuspid atresia, tetralogy of Fallot, Eisenmenger complex, persistent truncus arteriosus, and complete transposition of the great vessels. Differential diagnosis and principles of surgical therapy of these conditions. Sound, color, 30 minutes (1953). Procurable from The Film Center, University of Washington, Seattle 5, Washington, and from the American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

*CARDIAC ARRYTHMIAS

Robert H. Shuler, Mark F. Hance, Richard Shaw and David MacDougal, University of Chicago School of Medicine, Chicago, Illinois

A series of typical cardiac arrhythmias in experimental animals of the same types as encountered in clinical practices. Animations of abnormalities and typical EKG's shown. Silent, 30 minutes (1949). Procurable from Abbott Laboratories, North Chicago, Illinois.

*THE RECOGNITION AND MANAGEMENT OF RESPIRATORY ACIDOSIS

Reginald H. Smart, Hurley L. Motley and Joseph F. Boyle, University of Southern California School of Medicine, Los Angeles, California

This film depicts patients with respiratory acidosis whose condition is aggravated by injudicious treatment. Film then depicts the pathologic physiology involved and finally demonstrates the methods of treatment based upon physiologic principles. Sound, color, 30 minutes (1957). Procurable from Smith, Kline and French Laboratories, Philadelphia, Pennsylvania.

*MOVEMENTS OF THE CARDIAC VALVES AND ORIGIN OF HEART SOUNDS

H. L. Smith and H. E. Essex, Mayo Clinic, Rochester, Minnesota

Cardiac, aortic and pulmonic valves of isolated perfused heart of dog are shown in normal and slow motion. Simultaneous ECG and phonocardiographic records accompany activities of heart and valves. First and second sounds of heart are presented on sound track. Comments are on printed subtitles. Sound, color, 20 minutes (1955). Procurable from Mayo Clinic, Rochester, Minnesota.

ANESTHESIA

ETHER ANALGESIA FOR CARDIAC SURGERY

Joseph F. Artusio, Jr., New York Hospital, Cornell University Medical College, New York, N. Y.

This film demonstrates a technique which makes it possible to maintain a patient in analgesia throughout major cardiac surgery. Sound, color, 28 minutes (1955). Procurable from E. R. Squibb & Sons, 745 Fifth Avenue, New York, N. Y.

THE TECHNIC OF PERIDURAL ANESTHESIA FOR THORACIC SURGERY

Oral B. Crawford, Springfield, Missouri

This film portrays the technic of administering and managing peridural anesthesia in patients undergoing thoracotomy. Sound, color, 15 minutes (1953). Procurable from Astra Pharmaceutical Products, Inc., 7½ Neponset Street, Worcester, Massachusetts.

*ENDOTRACHEAL ANESTHESIA

Charles F. McCuskey, Los Angeles, California

Sound, color (1949). Procurable from E. R. Squibb & Sons, 745 Fifth Avenue, New York 22, N. Y.

EXTREMELY LIGHT ANALGESIA PLUS MUSCLE RELAXATION FOR MAJOR CARDIAC SURGERY

Seymour Schotz, Presbyterian Hospital, Philadelphia, Pennsylvania

Demonstrates the use of nitrous-oxide-oxygen analgesia and "Anectine" brand succinylcholine chloride in major cardiac surgery. Sound, color, 30 minutes (1956). Procurable from Burroughs Wellcome & Company, Inc., 1 Scarsdale Road, Tuckahoe 7, N. Y.

CARDIOVASCULAR SYSTEM

SURGICAL SECURITY DURING PATENT DUCTUS TRANSECTION

Osler A. Abbott, Emory University School of Medicine, Emory University, Georgia

Brief summary of history and methods used. X-ray case demonstration late leak of suture line by usual Pott's method. Diagrams of methods used. Outline of rationale for same. Demonstration of technique by color film. Salient points in operation on human case. Silent, color, 18 minutes (1956). Procurable from author.

ETHER ANALGESIA FOR CARDIAC SURGERY

Joseph F. Artusio, Jr., New York Hospital, Cornell University Medical College, New York, N. Y.

(See Anesthesia).

EXCISION OF POSTINFARCTION VENTRICULAR ANEURYSM

Edward E. Avery, Thomas W. Shields, Robert Hohf, Victor Bernhard and Craig Borden, Chicago, Illinois

The film illustrates the management of a patient with a large ventricular aneurysm following myocardial infarction. There is a brief description of history and physical findings and x-ray films are shown. The actual operation is shown whereby the neck of the aneurysmal sac is closed with multiple parallel mattress sutures, the sac excised, oversewn. Sound, color, 11 minutes (1956). Procurable from Edward E. Avery, M.D., 250 East Superior Street, Chicago 11, Illinois.

*TRANSPOSITION OF THE GREAT VESSELS

Thomas G. Baffes, and Willis J. Potts, Children's Memorial Hospital, Chicago, Illinois

Describes surgical technique for correcting transposition of the great vessels. Sound, color, 45 minutes (1958). Procurable from American College of Surgeons, 40 East Erie Street, Chicago, Illinois.

*THE SURGICAL TREATMENT OF MITRAL STENOSIS

Charles P. Bailey and Houck E. Bolton, Bailey Thoracic Clinic, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

The indications, contraindications for mitral commissurotomy, the preoperative and postoperative heart sounds and demonstration by means of the oscilloscope, electrocardiograms, x-ray findings, as well as the operative demonstration on autopsy specimens, and an actual operative procedure being carried out. Sound, color, 40 minutes (1954). Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut.

THE SURGICAL CORRECTION OF AORTIC STENOSIS

Charles P. Bailey and Houck E. Bolton, Bailey Thoracic Clinic, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

The transventricular approach for the surgical correction of aortic stenosis of rheumatic origin is demonstrated on an autopsy specimen and actual operative procedure is presented. The indication, the contraindications, preoperative heart sounds, as well as postoperative heart sounds are presented. The typical brachial artery pressure curves, x-ray findings and electrocardiographic findings are also presented. Sound, color, 40 minutes (1954). Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut.

*RESUSCITATION FOR CARDIAC ARREST

Claude S. Beck, University Hospitals, Cleveland, Ohio

Unpredictable cardiac arrest occurs several times each year in every large hospital. The purpose of this film is to help formulate a plan of action for such an emergency by presenting the basic principles of what might be called a "cardiac resuscitation fire [illegible] a dog heart, the steps in resuscitation of a heart in either standstill or in [illegible] Sound, color, 19 minutes (1956). Procurable from E. R. Squibb & Sons, 745 Fifth Avenue, New York, N. Y.

*SURGICAL TREATMENT OF CORONARY ARTERY DISEASE

Claude S. Beck, and David Leighninger, University Hospitals, Cleveland, Ohio

Illustrates electrical instability of the heart on a dog heart. An operation for the surgical treatment of coronary artery disease is demonstrated on a dog's heart and then on a human heart. The Mautz-Gregg Backflow method is demonstrated. Plastic-embedded and cleared hearts are shown. Sound, color, 28 minutes (1955). Procurable from Kenneth B. Wolfe, 2109 Adelbert Road, Cleveland, Ohio.

*PULMONARY ARTERIOVENOUS FISTULA

Albert Behrend, and Samuel Baer, Albert Einstein Medical Center, Yeshiva University, New York, N. Y.

Film showing a preoperative diagnostic study and multiple lobectomies in a case of pulmonary arteriovenous fistula involving both lungs. Silent, color, 20 minutes (1949). Procurable from Albert Behrend, M.D., 255 South 17th Street, Philadelphia, Pennsylvania.

*CREATION OF AN ARTIFICIAL DUCTUS IN THE TREATMENT OF TETRALOGY OF FALLOT

Alfred Blalock, Baltimore, Maryland

This demonstrates the creation of an artificial ductus arteriosis in the surgical treatment of tetrology of Fallot. The surgical therapy consists of an anastomosis between the right subclavian artery and the right pulmonary artery, thereby sending some of the improperly oxygenated blood in the aorta, to the lungs. Sound, color, 32 minutes (1953). Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut.

*SURGICAL TREATMENT OF TETRALOGY OF FALLOT

Alfred Blalock, Baltimore, Maryland

Shows an operation in which an anastomosis is performed between the right subclavian artery and the right pulmonary artery in the treatment of a six-year-old child with tetralogy of Fallot. Sound, color, 32 minutes (1954). Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut.

*BRONCHOVASCULAR ANATOMY

William E. Bloomer, A. A. Liebow and M. R. Hales, New Haven, Connecticut

(See Anatomy, etc.)

THE SURGICAL CORRECTION OF INTERATRIAL SEPTAL DEFECTS

Houck Bolton, Charles P. Bailey, and Henry Nichols, Bailey Thoracic Clinic, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

The indications and contraindications for a closed method of the treatment of interatrial septal defects called atriosepto-pexy is presented. The surgical technic is demonstrated and the results of such a method of surgical repair are discussed. Sound, color, 27 minutes (1957). Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut.

SURGICAL TREATMENT OF COARCTATION OF THE AORTA

David P. Boyd and H. D. Adams, Lahey Clinic, Boston, Massachusetts

Introduction to subject with x-rays and highlights of operative problems including approach exposure and technique of resection and repair. Silent, color, 20 minutes (1956). Procurable from Lahey Clinic, 605 Commonwealth Avenue, Boston 15, Massachusetts.

*SURGICAL TREATMENT OF CONGENITALLY ABSENT AORTIC ARCH

J. Maxwell Chamberlain, Roosevelt Hospital, New York, N. Y.

The film shows a congenitally absent aortic arch with only two vessels to the head and neck in a patient with hemiplegia from cerebral hypertension. A new arch was substituted. Patient is now three years postoperative and is participating in athletics. Silent, color, 10 minutes (1954). Procurable from author, 23 East 79th Street, New York, N. Y.

*THE USE OF SHUNTS IN AORTIC ARCH DISEASE

J. Maxwell Chamberlain, Fort Hamilton Veterans Hospital and Roosevelt Hospital, New York, N. Y.

This film has to do with resection of aneurysms of the arch of the aorta. Cerebral circulation is often embarrassed by surgery in this area and therefore shunts taken from 255 lb. pigs were used to by-pass the arch of the aorta in order to resect the aneurysms. Silent, color, 20 minutes (1955). Procurable from author, 23 East 19th Street, New York, N. Y.

*THE HEART: ELECTROKYMOGRAPHY, VENOUS CATHETERIZATION AND ANGIOCARDIOGRAPHY

W. Edward Chamberlain, Philadelphia, Lewis Dexter, Boston, and Marcy L. Sussman, New York

Sound, color, 28 minutes (1951). Procurable from G. D. Searle & Company, P. O. Box 5110, Chicago 80, Illinois.

SURGICAL REMOVAL MYXOMA LEFT AURICLE SIMULATING MITRAL STENOSIS

Denton A. Cooley and George C. Morris Jr., Baylor University College of Medicine, Houston, Texas

Myxoma of the left auricle is the most common intracavitary tumor of the heart. This lesion may produce findings similar to mitral stenosis and diagnosis is usually made at exploratory cardiotomy. This film demonstrates successful removal of two such lesions in patients in whom a diagnosis of mitral stenosis had been made prior to operation. Sound, color, 15 minutes (1958). Procurable from Baylor University College of Medicine, Houston 25, Texas.

REPAIR AORTICO-PULMONARY SEPTAL DEFECT DURING CARDIOPULMONARY BY-PASS

Denton A. Cooley, Baylor University College of Medicine, Houston, Texas

Aortico-pulmonary septal defect or aortic window is an uncommon lesion producing left to right circulatory shunt. In the past surgical treatment has presented a formidable mortality. This film presentation demonstrates the use of a pump oxygenator and cardiopulmonary by-pass for safe conduct of operative correction of this defect. Sound, color, 16 minutes (1957). Procurable from Baylor University College of Medicine, Houston 25, Texas.

EXTRACORPOREAL CIRCULATION IN SURGICAL TREATMENT OF VENTRICULAR AND ATRIAL SEPTAL DEFECTS

Denton A. Cooley and Joseph R. Latson, Baylor University College of Medicine, Houston, Texas

Film demonstrates a method of cardiopulmonary by-pass for open heart surgery using a pump oxygenator. Two types of bubble diffusion oxygenator are shown, one a disposable plastic device and the other made of stainless steel. Induced cardiac arrest using potassium citrate is demonstrated for repair of ventricular septal defects and repair of atrial defects is also shown. Sound, color, 22 minutes (1957). Procurable from Baylor University College of Medicine, Houston 25, Texas.

CLOSURE OF ATRIAL SEPTAL DEFECT UNDER HYPOTHERMIA

Denton A. Cooley, Baylor University College of Medicine, Houston, Texas

Surgical repair of atrial septal defect may be accomplished by both closed and open cardiac techniques, depending upon certain anatomic physiologic features of the lesion. Although in simple defects located in a high septal position, closed methods are effective and satisfactory, in many instances repair under direct vision is desirable and occasionally necessary. This film demonstrates the method of open cardiotomy under general body hypothermia for repair of an atrial defect in a ten-year-old girl with temporary caval inflow occlusion. Sound, color, 11 minutes (1956). Procurable from author.

METHODS OF SURGICAL TREATMENT OF PULMONIC STENOSIS

Denton A. Cooley and Dan G. McNamara, Baylor University College of Medicine, Houston, Texas.

This film demonstrates several methods of surgical treatment of congenital pulmonic stenosis and explains the method of selection of the method based upon anatomic findings in the heart. Closed transventricular valvulotomy, hypothermia, and cardiopulmonary by-pass are shown with a description of technic for each method. Sound, color, 18 minutes (1956). Procurable from Baylor University College of Medicine, Houston 25, Texas.

TOTAL EXCISION OF THE AORTIC ARCH FOR ANEURYSM

Denton A. Cooley and Michael E. DeBakey, Baylor University College of Medicine, Houston, Texas

The film demonstrates a method of excision of total aortic arch using temporary shunts sutures to ascending aorta, descending aorta and carotid arteries. After excision and replacement of the arch with a graft, the shunt was removed. Sound, color, 17 minutes (1955). Procurable from Baylor University College of Medicine, Houston 25, Texas.

CLOSURE OF INTERVENTRICULAR SEPTAL DEFECT UTILIZING CARDIAC ARREST

Philip Crastnopol, Alvin A. Bakst, H. Gianfrencesco, E. A. Braunstein and Irving G. Kroop, Jewish Hospital of Brooklyn, Brooklyn, New York

The film demonstrates the surgical technique for the closure of ventricular septal defects. This includes cannulation of the canal and subclavian artery; the production of cardiac arrest; the repair of the defect; and the resumption of normal cardiac rhythm. Silent, color, 12 minutes (1958). Procurable from Alvin A. Bakst, M.D., 135 Eastern Parkway, Brooklyn, New York.

*SURGICAL TREATMENT OF DISSECTING ANEURYSM

Michael E. DeBakey, Denton A. Cooley and Oscar Creech, Jr., Baylor University College of Medicine, Houston, Texas

This film is concerned with surgical treatment of dissecting aneurysm of the aorta. Two cases are presented illustrating the two most common forms of the disease: First, the type in which dissection begins in the ascending aorta; second, the type in which dissection begins at or below the level of the left subclavian artery. Clinical manifestations and diagnostic features for both conditions are presented. The technic of the surgical procedure employed in each case is illustrated in detail, including diagrammatic drawings to emphasize the special technical features of the problem. Sound, color, 18 minutes (1955). Procurable from Baylor University College of Medicine, Houston 25, Texas.

*ANEURYSMS OF THE ABDOMINAL AORTA. SURGICAL CONSIDERATIONS BASED UPON ANALYSIS OF 350 RESECTED CASES

Michael E. DeBakey, Denton A. Cooley and E. Stanley Crawford, Baylor University College of Medicine, Houston, Texas

This film is concerned with surgical considerations of aneurysms of the abdominal aorta based upon experience with 350 cases treated by resection and replacement by aortic homografts and various plastic substitutes. Certain characteristic clinical, pathologic, and diagnostic features of these aneurysms are presented and illustrated. Emphasis is placed upon technical considerations in the resection and replacement of the aneurysm showing the use of both aortic homografts and prosthetic tubes made of plastic materials such as nylon and dacron. The indications and contraindications to operation and the factors influencing mortality are also presented. Sound, color, 26 minutes (1957). Procurable from Baylor University College of Medicine, Houston 25, Texas.

*THORACOABDOMINAL ANEURYSM INVOLVING CELIAC, SUPERIOR MESENTERIC AND RENAL ARTERIES. RESECTION AND HOMOGRAFT REPLACEMENT

Michael E. DeBakey, Oscar Creech, Jr., Denton A. Cooley and George C. Morris, Jr., Baylor University College of Medicine, Houston, Texas

This film portrays the resection of an aneurysm of the thoracoabdominal aorta involving the celiac, superior mesenteric and renal arteries. The method by which the aneurysm is resected and replaced with a homograft with restoration of continuity to these major branches is illustrated both by animated diagrams and by views of the actual operative procedure. Sound, color, 21 minutes (1957). Procurable from Baylor University College of Medicine, Houston 25, Texas.

SURGICAL TREATMENT OF SACCIFORM ANEURYSMS OF ASCENDING AORTA, TANGENTIAL EXCISION OF LATERAL AORTORRHAPHY

Michael E. DeBakey and Denton A. Cooley, Baylor University College of Medicine, Houston, Texas

Excisional treatment of aortic aneurysms is the method of choice wherever conditions permit its satisfactory application. The actual surgical approach, however, varies, depending upon the nature and location of the lesion. This film demonstrates a method suitable for sacciform aneurysms of the ascending aorta without necessitating interruption of aortic flow. Sound, color, 15 minutes (1955). Procurable from Baylor University College of Medicine, Houston 25, Texas.

CLOSURE OF CONGENITAL INTERAURICULAR SEPTAL DEFECT BY THE "CIRCUMCLUSION TECHNIC OF SONDERGAARD"

Paul T. DeCamp, New Orleans, Louisiana

An anatomical dissection as shown and a clinical operation recorded to demonstrate the anatomy and the operative technic of this method of closure of congenital interatrial septal defects. Sound, color, 17 minutes (1956). Procurable from author, Ochsner Clinic, 3505 Prytania Street, New Orleans 15, Louisiana.

EARLY PERICARDECTOMY IN TUBERCULOSIS PERICARDITIS

R. A. Dillard and Rex B. Perkins, Veterans Administration Hospital, Birmingham, Alabama

This film emphasizes the place of early pericardectomy in the effusive stage of tuberculous pericarditis. A patient illustrating this is shown, including preoperative study, operation and postoperative course. Sound, color, 20 minutes (1956). Procurable from Veterans Administration Central Office, Vermont Avenue and H Street, N.W., Washington 25, D. C.

ELECTIVE CARDIAC ARREST

Donald B. Effler, Laurence K. Groves and Harold F. Knight, Jr., Cleveland Clinic Foundation, Cleveland, Ohio

Pictorial description of the Melrose technique for elective cardiac arrest with potassium citrate and clinical examples. Sound, color, 20 minutes (1957). Procurable from Cleveland Clinic Foundation, 2020 East 93rd Street, Cleveland 6, Ohio.

CLOSURE OF INTERVENTRICULAR SEPTAL DEFECT USING THE PUMP OXYGENATOR

J. L. Ehrenhaft, State University of Iowa Hospitals, Iowa City, Iowa

Closure of an interventricular septal defect in an eight-year-old boy is shown The extracorporeal machine is a DeWall type pump oxygenator The operative procedure, open cardiotomy, closure of interventricular septal defect using coronary return, in this instance is beautifully demonstrated The extracorporeal circuit is also shown in a schematic manner The method of cannulization of superior and inferior venae cavae and left subclavian artery is well demonstrated Silent, color, 14 minutes (1956) Procurable from author.

CLOSURE OF INTERATRIAL SEPTAL DEFECT USING HYPOTHERMIA

J. L. Ehrenhaft, State University of Iowa Hospitals, Iowa City, Iowa

Closure of large ostium secundum defect in a fourteen-year-old girl The technique of cooling in an ice bath, thoracotomy, open cardiotomy, closure of interatrial septal defect under direct vision and rewarming of the patient is shown Silent, color, 14 minutes (1956). Procurable from author

SELECTIVE CARDIAC ARREST IN OPEN HEART SURGERY

William H. Falor, Clifford Boeckman and John Vallee, Akron, Ohio

In the authors' laboratory, in open right heart surgery employing an extracorporeal circuit for periods in excess of 30 minutes, a significant decrease in survival follows if the beating heart is arrested by potassium Cardiac arrest, however, may be mandatory for the repair of certain defects Selective cardiac arrest reconciles the increased potential survival of nonarrest techniques with the occasional necessity for arrest methods In the technique of selective cardiac arrest exploratory right cardiotomies are made with the heart beating Readily reparable lesions are treated without arrest, less accessible lesions or those obscured by hemorrhage are repaired after arrest is induced The movie outlines the rationale for, and depicts the technical production of selective cardiac arrest Sound, color, 11 minutes (1957). Procurable from William H Falor, M D , 159 South Main Street, Akron 8, Ohio

*CARDIAC ARREST: ITS PREVENTION, RECOGNITION AND TREATMENT

Egbert H. Fell and Lowell Peterson, Chicago, Illinois

The film shows graphically the effects to the heart of an obstructed airway and the importance of an open airway with free exchange of gases Sound, color, 17 minutes (1953). Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut

COMMISSUROTOMY OF MITRAL STENOSIS

Carmelo Gil-Turner, Grupo Sanatorial de Santa Marina, Bilbao, Spain

This film shows the practice of a commissurotomy for mitral stenosis, performed through anterior thoracic incision and the dilatation of the valve by introducing the index finger in the left auricle The type of valvulotome used when necessary is also shown Silent, color, 15 minutes (1954) Procurable from author, Clinica F San Sebastian, Rafaela de Ybarra 25, Deusto-Bilbao, Spain

THE MITRAL VALVE—DYNAMIC PATHOLOGY AND SURGERY

Robert P. Glover, Julio C. Davila and Robert G. Trout, Philadelphia, Pennsylvania

The film demonstrates the action of the mitral valve in normal and disease states An attempt is made to point out mechanical impairments resulting from rheumatic heart pathology compared to the normal It includes demonstrations of techniques for surgical correction of mitral stenosis and insufficiency Sound, color, 14 minutes (1957) Procurable from E R Squibb & Sons, 745 Fifth Avenue, New York, N Y

THE ANATOMIC BASIS FOR THE SURGICAL CORRECTION OF MITRAL INSUFFICIENCY

Robert P. Glover, Julio C. Davila and Robert G. Trout, Philadelphia, Pennsylvania

This film attempts to elucidate visually the anatomic alterations affecting the mitral valve which leads to mitral insufficiency The various surgical techniques for the correction of mitral insufficiency are illustrated indicating the anatomic and mechanical effectiveness of each These pictures are taken by photographing the valve of autopsy specimens while the ventricular contraction is simulated by means of a mechanical pulse duplicator Sound, color, 13 minutes (1957). Procurable from Medical Illustrator, The Presbyterian Hospital, 39th Street and Powelton Avenue, Philadelphia, Pennsylvania

*SURGICAL MANAGEMENT OF MITRAL STENOSIS COMPLICATED BY PERIPHERAL EMBOLI

Alfred Goldman, Beverly Hills, California

Film contains history of a patient, his x-rays, operation, gross pathology, microscopic pathology of specimen and auricle and thrombus Technique of obtaining direct pressures of left auricle, left ventricle, and pulmonary veins is also included Pre- and post-operative cardiac catheterization study is included Follow-up x-rays and follow-up of patient Film is documented by slow motion taken at 200 frames per second of auricular flutter and auricular fibrillation Silent, color, 26 minutes (1952) Procurable from author, 416 North Bedford Drive, Beverly Hills, California

CARDIAC BY-PASS AND ELECTIVE ARREST WITH AUTOGENOUS OXYGENATION

James A. Helmsworth, William R. Cole, James Neely and Ralph Shabetai, University of Cincinnati College of Medicine, Cincinnati, Ohio

The technique of cannulation is given for complete cardiac by-pass Autogenous oxygenation is made possible by innovations in pulmonary artery cannulation and pulmonary vein drainage The Melrose technique is employed for arrest with potassium citrate Exploration of the heart is demonstrated through incision in the right ventricle (The film is concerned entirely with experimental work in progress) Silent, 15 minutes (1957) Procurable from James A Helmsworth, M D , 3231 Burnet Avenue, Cincinnati 29, Ohio

*DEVELOPMENT OF THE AORTIC ARCH

George H. Humphreys II, Columbia-Presbyterian Medical Center, New York, N. Y.

(See Anatomy, etc)

*ANOMALIES OF THE AORTIC ARCH

George H. Humphreys II, Columbia-Presbyterian Medical Center, New York, N. Y.

(See Anatomy, etc)

*DEVELOPMENT OF THE HEART

George H. Humphreys II, Columbia-Presbyterian Medical Center, New York, N. Y.

(See Anatomy, etc.)

*PATENT DUCTUS ARTERIOSUS—PHYSIOLOGY, DIAGNOSIS AND CLINICAL CONSIDERATIONS

George H. Humphreys II, Columbia-Presbyterian Medical Center, New York, N. Y.

This film is in two parts. The first part shows physiologic and diagnostic factors illustrated by animated diagrams. The second part shows the diagnosis and surgical correction of a case. Sound, color, 25 minutes (1952). Procurable from E. R. Squibb & Sons, 745 Fifth Avenue, New York, N. Y.

*SURGICAL TREATMENT FOR CONGENITAL PULMONARY VALVULAR STENOSIS

George H. Humphreys II, New York, N. Y.

Pulmonary valvultotomy (Brock's procedure) is shown as performed on a seven-year-old child with valvular stenosis. Sound, color, 20 minutes (1951). Procurable from Sturgis-Grant Productions, Inc., 322 East 44th Street, New York, N. Y.

*TECHNIQUES IN ANGIOGRAPHY

A. W. Humphries, Cleveland, Ohio

The film is divided into two parts: Part I demonstrates the techniques of aortography, and Part II the techniques of femoral arteriography. Each section follows the same pattern of demonstration of equipment, demonstration of procedure by animation, demonstration of procedure in actual practice, and illustrative angiograms, and, finally, a listing of the equipment required. Sound, color, 14 minutes (1957). Procurable from author, 2020 East 93rd Street, Cleveland 6, Ohio, or American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

SURGICAL CORRECTION OF CYANOSIS DUE TO INSERTION OF LEFT SUPERIOR VENA CAVA INTO LEFT AURICLE

Elliott S. Hurwitt, Montefiore Hospital, New York, N. Y.

Cyanosis due to insertion of a large systemic vein into the left auricle is corrected by ligation of the anomalous vessel. Silent, color, 6 minutes (1955). Procurable from author.

*FUNCTION OF THE MITRAL VALVE IN SITU

Elliott S. Hurwitt and Adrian Kantrowitz, Montefiore Hospital, New York, N. Y.

Shows slow motion views of the mitral area in situ, free of blood while artificial heart takes on function of left heart. Sound, color, 13 minutes (1952). Procurable from the American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

RESECTION OF ANEURYSM OF THORACOABDOMINAL AORTA

Elliott S. Hurwitt, Montefiore Hospital, New York, N. Y.

An Aneurysm of the thoracoabdominal aorta, including the celiac and superior mesenteric arteries, with rupture into the psoas muscle, was resected and replaced by a homograft. A temporary by-pass shunt was employed. Sound, Color, 7 minutes (1956). Procurable from author.

*TETRALOGY OF FALLOT

John C. Jones, University of Southern California School of Medicine, Los Angeles, California

First, the anatomic features of tetralogy of Fallot are explained by a series of medical illustrations of the embryonic development of the heart. Then two operations using the Blalock-Taussig procedure are shown, and two using the Potts-Smith anastomosis. Sound, color, 33 minutes (1954). Procurable from E. R. Squibb & Sons, 745 Fifth Avenue, New York 22, N. Y.

*ACTION OF THE HUMAN HEART VALVES

Karl P. Klassen and C. V. Meckstroth, Ohio State University Health Center, Columbus, Ohio

(See Anatomy, etc.)

CLOSURE OF INTERVENTRICULAR SEPTAL DEFECT WITH INDUCED CARDIAC ARREST

Conrad R. Lam, Thomas Gahagan, Charles Sergeant and Edward Green, Henry Ford Hospital, Detroit, Michigan

The film shows the closure of a large interventricular septal defect in a seven-year-old boy. Open cardiotomy is carried out during cardiac by-pass with a pump-oxygenator of the bubble type. Before the ventriculotomy, cardiac arrest is produced by the injection of acetylcholine into the aorta, from which it passed into the coronary arteries. Sound, color, 25 minutes (1956). Procurable from Conrad R. Lam, Henry Ford Hospital, Detroit, Michigan.

LEFT HEART CATHETERIZATION

G. H. Lawrence, Mason Clinic, Seattle, Washington

Technic, indications and interpretation of percutaneous trans-thoracic left catheterization. Color, 10 minutes (1957). Procurable from author, 1118 Ninth Avenue, Seattle, Washington.

*THE ANATOMICAL CORRECTION OF THE TETRALOGY OF FALLOT DEFECTS UNDER DIRECT VISION, UTILIZING THE PUMP OXYGENATOR

C. Walton Lillehei, Richard A. DeWall, Herbert E. Warden and Richard L. Varco, University of Minnesota Medical School, Minneapolis, Minnesota

This film shows the complete correction of the tetralogy of Fallot defects utilizing open cardiotomy with the pump oxygenator. Closure of the ventricular septal defect and correction of the pulmonic stenosis by infundibular resection and pulmonary valvulotomy is portrayed. The pump oxygenator utilized is portrayed and induced cardiac asystole was utilized to facilitate the reparative surgery. This tetralogy patient also had an unusual associated defect, a ruptured aneurysm of the sinus of Valsalva, the repair of which is shown. Sound, color, 24 minutes (1957). Procurable from Audio-Visual Service, University of Minnesota, Minneapolis, Minnesota.

*MITRAL COMMISSUROTOMY

John L. Madden, St. Clare's Hospital, New York, N. Y.

This film shows the technic for "finger-fracture" of a stenotic mitral valve orifice, a procedure which the author has found to be of value in selected cases Sound, color, 25 minutes (1952) Procurable from E R. Squibb & Sons, 745 Fifth Avenue, New York, N Y

*A SIMPLE OPERATION FOR CORONARY INSUFFICIENCIES

M. S. Mazel, Edgewater Hospital, Chicago, Illinois

This film shows the pathology of coronary occlusion, as well as the technique of operation and how the procedure increases the blood supply of the myocardium by formation of a granulomatous pericarditis which acts as a source of collateral blood supply from the pericardial and epicardial regions Silent, color, 30 minutes (1956) Procurable from author, 5700 North Ashland Avenue, Chicago 26, Illinois

*A SIMPLE OPERATION FOR REVASCULARIZATION OF THE MYOCARDIUM IN CORONARY HEART DISEASE

M. S. Mazel, Edgewater Hospital, Chicago, Illinois

The film demonstrates the modification of Dr Thompson's technique of revascularization of the myocardium for ischemia due to coronary heart disease by means of distributing U S P talc (magnesium silicon) within the pericardium Indications for this operation are enumerated and electrocardiograph tracings of cases operated are demonstrated as well as histological sections of normal pericardium, revascularized pericardium and autopsy specimens of patients dying of other causes, having been revascularized by this method Silent, color, 30 minutes (1954) Procurable from author, 5700 North Ashland Avenue, Chicago 26, Illinois

*ROENTGEN DEMONSTRATION OF MITRAL AND AORTIC INSUFFICIENCY

Howard L. Moscovitz and Robert J. Wilder, Mt. Sinai Hospital, New York, N. Y.

Radiopaque dye is injected into the left side of the heart and extremely rapid (48 frames per second) motion picture films are made of a fluoroscopic screen whose image is intensified one thousand times The reflux of dye through incompetent mitral and aortic valves is shown in addition to the details of normal valve function Silent, 10 minutes (1956). Procurable from Howard L Moscovitz, M D , Mt Sinai Hospital, 1 East 100th Street, New York 29, N Y

*CHRONIC CONSTRICTIVE PERICARDITIS

Emil A. Naclerio, Harlem and Columbus Hospitals, New York, N. Y.

The etiology, pathogenesis and various pathologic types of chronic constrictive pericarditis are briefly considered The major diagnostic features of an elderly woman who was operated upon are briefly discussed The operative procedure and result are shown The operative technique in the same patient is shown Silent color, 18 minutes (1948) Procurable from author, 35 East 35th Street, New York 16, N. Y.

*CONGENITAL PULMONARY STENOSIS WITH INTACT INTERVENTRICULAR SEPTUM

Willis J. Potts, William L. Riker and Stanley Gibson, Children's Memorial Hospital, Chicago, Illinois

Diagnostic features are briefly set forth and the pathology is illustrated The operative technic of transventricular valvulotomy and dilatation of the stenosed pulmonary valve is pictured in detail Silent, color, 32 minutes (1953) Procurable from American College of Surgeons, 40 East Erie Street, Chicago, Illinois

*AORTIC PULMONARY ANASTOMOSIS FOR PULMONARY STENOSIS

Willis J. Potts, Children's Memorial Hospital, Chicago, Illinois

The salient points for a diagnosis of tetralogy of Fallot are reviewed The technique of aortic pulmonary anastomosis is illustrated in detail and clarified by animation Silent, color, 27 minutes (1949) Procurable from American College of Surgeons, 40 East Erie Street, Chicago, Illinois

*SURGICAL DIVISION OF THE PATENT DUCTUS ARTERIOSUS

Willis J. Potts, Children's Memorial Hospital, Chicago, Illinois

This film reviews briefly the symptoms of patent ductus Most of the emphasis is placed upon the technique of division and suture of the ductus by means of the Potts toothed clamps Silent, color, 25 minutes (1951) Procurable from American College of Surgeons, 40 East Erie Street, Chicago, Illinois

CONGENITAL DIVERTICULUM OF THE LEFT VENTRICLE

Willis J. Potts and Arthur DeBoer, Children's Memorial Hospital, Chicago, Illinois

An unusual case of congenital diverticulum of the left ventricle protruding in the epigastric space is pictured The operative procedure of removing the diverticulum and closing the stump of the ventricle is shown Recovery was complete Silent color, 17 minutes (1952). Procurable from American College of Surgeons, 40 East Erie Street Chicago Illinois

A SYNDROME OF CONGENITAL DEFECTS INVOLVING THE ABDOMINAL WALL, DIAPHRAGM, STERNUM, HEART AND PERICARDIUM

Mark M. Ravitch, The Johns Hopkins School of Medicine, Baltimore, Maryland

The film shows the correction of the ventral defect in a patient representative of the specific syndrome in which there are associated congenital defects including a ventral abdominal defect, a split or deficient lower sternum a deficient anterior and central portion of the diaphragm, a deficiency of the distal half of the pericardium and an interventricular septal defect Silent, color, 15 minutes Procurable from author

*RIGHT HEART CATHETERIZATION

Mr. James Reske and Paul S. Mahoney, University of California School of Medicine, Los Angeles, California

Heart catheterization procedure specifically directed to x-ray and laboratory technicians, general practitioners and medical students Sound color, 19 minutes (1957) Procurable from Du Pont Company, Los Angeles, California

*CONGENITAL MALFORMATIONS OF THE HEART (PART I: DEVELOPMENT OF THE NORMAL HEART)

Robert F. Rushmer and Richard J. Blandau, University of Washington, Seattle, Washington

(See Anatomy, etc.)

*CONGENITAL MALFORMATIONS OF THE HEART (PART II: ACYANOTIC CONGENITAL HEART DISEASE)

Robert F. Rushmer, University of Washington, Seattle, Washington

(See Anatomy, etc.)

*CONGENITAL MALFORMATIONS OF THE HEART: (PART III: CYANOTIC CONGENITAL HEART DISEASE)

Robert F. Rushmer, University of Washington, Seattle, Washington

(See Anatomy, etc.)

*EXTREMELY LIGHT ANALGESIA PLUS MUSCLE RELAXATION FOR MAJOR CARDIAC SURGERY

Seymour Schotz, Presbyterian Hospital, Philadelphia, Pennsylvania

(See Anesthesia.)

*VALVULOTOMY FOR VALVULAR PULMONIC STENOSIS, DIRECT VISUAL PROCEDURE WITH HYPOTHERMIA

H. William Scott, Jr., Nashville, Tennessee

Sound, color, 26 minutes (1955). Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut.

BY-PASS AORTIC POPLITEAL GRAFT

Andrew G. Sharf, Glendale, California

The purpose of this movie is to demonstrate utilization of by-pass aortic graft in patients with chronic obliterative arterial disease. It demonstrates the value of preoperative arteriogram, showing both the value of preoperative arteriogram, showing both the aorta and distal arteries of the lower extremities. The movie also shows anastomosis of the popliteal arteries prior to performance of the entire procedure. It illustrates the importance of preservation of each collateral vessel in the dissection of the main artery and the site of anastomosis. The utilization of modified hypothermia for this type of surgery is indicated, and the method of utilizing a previously prepared homograft is demonstrated. For the sake of expediency, surgery is performed by two teams. Silent, color, 13 minutes (1956). Procurable from author, 932 South Central Avenue, Glendale 4, California.

CARDIOPNEUMOPEXY: A SURGICAL METHOD OF REVASCULARIZATION OF THE ISCHEMIC MYOCARDIUM

Franklin R. Smith, Seattle, Washington

The first portion shows the experimental data and technic and then two operations on pateints are depicted, showing the technical steps in carrying out a cardiopneumopexy. There is adequate description of the indications and results. Silent, color, 24 minutes (1956). Procurable from author, 942 Medical Dental Bldg., Seattle, Washington.

*MOVEMENTS OF THE CARDIAC VALVES AND ORIGIN OF HEART SOUNDS

H. L. Smith and H. E. Essex, Mayo Clinic, Rochester, Minnesota

(See Anatomy, etc.)

*HEART CATHETERIZATION AND CARDIOANGIOGRAPHY

F. Mason Sones, Jr., Cleveland Clinic Foundation, Cleveland, Ohio

Films taken with image amplifier at 50-54 frames per second demonstrate catheterization and selective cardioangiography in all major cyanotic and non-cyanotic congenital heart lesions. Silent, 40 minutes (1956). Procurable from author.

*PROCEDURES IN THE DIAGNOSIS OF CARDIOVASCULAR DISEASE

University of Southern California School of Medicine, Los Angeles, California

This film for the general medical profession, interns, and medical students, takes a patient from initial physical examination through a complete diagnosis. Using x-ray photography, it reviews all the latest techniques of cardiovascular diagnosis. Cardiac catheterization, vectorcardiogram, phonocardiogram ballistocardiogram, besides the usual cardiac diagnostic technique, are demonstrated in the film. Sound, color, 32 minutes (1952). Procurable from University of Southern California, Los Angeles 7, California

PERICARDIECTOMY FOR CONSTRICTIVE PERICARDITIS

Allan Stranahan, Ralph D. Alley and Harvey W. Kausel, Albany Hospital and Medical College, Albany, N. Y.

Classical case of constrictive pericarditis with total pericardiectomy via a bilateral, trans-sternal thoracotomy approach. Silent, color, 16 minutes (1955). Procurable from Allan Stranahan, M.D., Albany Medical College, Albany, N. Y.

PULMONARY ARTERIOVENOUS ANEURYSM

Lawrence H. Strug and William Leon, New Orleans, Louisiana

The film portrays a patient who has an arteriovenous aneurysm of the right middle lobe of the lung. It also shows pictures of the patient, x-rays and the degree of cyanosis which occurred, as well as preoperative angiocardiogram and oxygen studies. The operative procedure is shown, and the pulsations of the aneurysm well demonstrated. X-rays, blood oxygen studies and the patient are shown postoperatively. Sound, color, 17 minutes (1955). Procurable from American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

VISUAL REPAIR OF CONGENITAL AORTIC AND PULMONARY STENOSIS

Henry Swan, Denver, Colorado

Open operation on the stenotic aortic and pulmonary valves of two patients is demonstrated and the methods discussed. Sound, color, 22 minutes (1957). Procurable from author, 4200 East 9th Avenue, Denver, Colorado.

VISUAL SURGERY IN THE OPEN HEART DURING HYPOTHERMIA

Henry Swan, Denver, Colorado

Shows patient being cooled in a tub of ice water in preparation for open heart surgery. Three such procedures are demonstrated. Sound, color, 26 minutes (1953). Procurable from author, 4200 East Ninth Avenue, Denver 7, Colorado.

*CARDIAC ARREST

Henry Swan and J. Cuthbert Owens, Denver, Colorado

A typical episode of cardiac arrest occurring in the operating room, together with the method of management of this acute catastrophe, is demonstrated. Silent, color, 30 minutes (1953). Procurable from Henry Swan, M.D., 4200 E. 9th Ave. Denver Colorado, and Medical Audio Visual Institute, 185 North Wabash Avenue, Chicago, Illinois.

MITRAL COMMISSUROTOMY

John V. Thompson and E. R. Eaton, Methodist Hospital, Indianapolis, Indiana

The film demonstrates the anatomy and the technique of mitral commissurotomy. Sound, color, 10 minutes (1957). Procurable from John V. Thompson, M.D., 7899 Ridge Road, Indianapolis, Indiana.

*CONVERSION OF THE AURICULAR APPENDAGE INTO A LEAK-PROOF VALVE TUBE FOR INTRACARDIAC SURGERY

Samuel A. Thompson, New York Medical College, New York, N. Y.

Actual operation upon experimental animals showing conversion of auricular appendage into a two-way valve. Silent, color, 20 minutes (1951). Procurable from New York Medical College, New York, N. Y.

CLOSURE OF VENTRICULAR SEPTAL DEFECT UNDER VISION USING DE WALL OXYGENATOR

Richard L. Varco, University of Minnesota, Minneapolis, Minnesota

This material describes the technical aspects involved in direct vision closure of a ventricular septal defect using a bubble-type oxygenator. The precise cannulations and intracardiac steps are detailed so that by means of the narration and the close-up photography, the individual manipulations are clearly represented. Sound, color, 18 minutes (1956). Procurable from Audio Visual Education Service, University of Minnesota, Minneapolis 14, Minnesota.

*PERIPHERAL CIRCULATION-PLETHYSMOGRAPHIC OBSERVATIONS

Travis Winsor, Los Angeles, California

A short dissertation on the history of the peripheral circulation is presented along with a rather detailed study of modern methods for studying the status of the circulation. Plethysmographic tracings and their meanings are discussed. The value of the plethysmograph as another means to study the adequacy of the peripheral circulation prior to other operative procedures and the use of this instrument are vividly portrayed. Sound, color, 25 minutes (1957). Procurable from Ciba Pharmaceutical Products Inc., 556 Morris Avenue, Summit, New Jersey and Ideal Pictures Corporation, 58 East South Water Street, Chicago 1, Illinois.

*CLOSURE OF ATRIAL SEPTAL DEFECT IN THE BLOODLESS HYPOTHERMIC HEART

Helge B. Wulff, Knut Haeger and Björn Sjöstrom, Malmo General Hospital, University of Lund, Malmo, Sweden

The film shows closure of a large atrial septum defect in a girl aged twelve. The body temperature was reduced to 25° C. in a thermobox. The thorax was opened by a transverse incision in the fourth intercostal space with splitting of the sternum. The azygos vein was ligated, the superior inferior vena cava and lung hilii were clamped. After the right auricle had been opened and the diagnosis checked by insertion of a finger the incision in the auricle was closed. Stay sutures were placed in the right atrium. The atrial wall was clamped and the atrium incised. The superior inferior vena cava and lung hilii were then occluded and sixty seconds later the aorta and the pulmonary artery. The atrium was opened and the septal defect sutured with seven silk stitches. The atrial wall was then sutured and blood gradually allowed to enter after removal of the clamps occluding the aorta and the pulmonary artery. Electrocardiograms and diagrams of the blood potassium level and pH-values during the operation are shown. The patient is demonstrated. Silent, color, 13 minutes (1956). Procurable from Malmo General Hospital, Malmo, Sweden.

ESOPHAGUS

ESOPHAGEAL REPLACEMENT UTILIZING COLON AND JEJUNAL INTERPOSITION

Osler A. Abbott and William H. Sewell, Emory University School of Medicine, Emory University, Georgia

Outline of problem emphasizing long-term complications from esophagogastrostomy. Diagrammatic representation of technical steps in a) use right colon in substernal tunnel to replace entire thoracic esophagus, b) use jejunum to replace lower ⅓ esophagus. Pictures actual operation for same. Pre- and post-operative x-ray studies. Silent, color, 23 minutes (1957). Procurable from author.

SURGICAL TREATMENT OF HIATAL HERNIA

Brian B. Blades, Washington, D. C.

Sound, color, 28 minutes (1954). Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut.

SURGICAL MANAGEMENT OF THE COMPLICATIONS OF REFLUX ESOPHAGITIS

F. Henry Ellis Jr., Mayo Clinic, Rochester, Minnesota

The film discusses the etiology of reflux esophagitis, the complications of reflux esophagitis, and the various operative procedures available for its treatment. The operation of esophagogastrectomy and antral excision is shown and its rationale discussed. Sound, color, 17 minutes (1957). Procurable from Mayo Clinic, Rochester, Minnesota.

ESOPHAGEAL RECONSTRUCTION WITH COLON TRANSPLANT

Paul F. Fox and David S. Jones, Chicago, Illinois

This picture illustrates construction of the esophagus by detaching a segment of upper colon and swinging it on its vascular supply from the midcolic artery to a retrosternal position, where the upper end is anastomosed to the esophagus in the neck and the lower end to the stomach. Color, 21 minutes (1956). Procurable from Stritch School of Medicine of Loyola University, 706 South Wolcott Avenue, Chicago 12, Illinois.

*PEDUNCULATED POLYPOID LIPOMA ORIGINATING AT INTROITUS OF ESOPHAGUS AND EXTENDING TO CARDIA

Stuart W. Harrington, Mayo Clinic, Rochester, Minnesota

Transpleural esophagotomy with complete removal of large tumor (22 cms. in length and weighing 570 gms.) that was causing dilatation of esophagus and displacing trachea. Silent, color, 17 minutes (1944). Procurable from Mayo Clinic, Rochester, Minnesota.

THE USE OF A GASTRIC TUBE TO REPLACE OR BY-PASS THE ESOPHAGUS

Henry J. Heimlich, New Rochelle, N. Y.

A tube is created from the greater curvature of the stomach and remains attached at the cardia. The spleen is resected distal to the origin of the left gastroepiploic vessels which nourish the tube. The tube is reversed and the antral end is brought cephalad and anastomosed to the pharynx or cervical esophagus. Four-fifths of the stomach remains in its normal position in the abdomen retaining its storage function. Sound, color, 30 minutes (1956). Procurable from author, 140 Lockwood Avenue, New Rochelle, N. Y.

*ESOPHAGOSCOPIC VIEWS OF LESIONS OF THE ESOPHAGUS

Paul H. Holinger and Kenneth C. Johnston, Chicago, Illinois

Views of lesions of the esophagus are shown as they appear through the esophagoscope. Benign stenosis, both congenital and acquired, cardiospasm, postsurgical strictures of the esophagus, and benign and malignant tumors are shown without extensive case histories. Superficial and deep esophageal varicies and foreign bodies are seen as they are visualized through the esophagoscope. In occasional cases the x-ray studies precede the esophagoscopic view. Silent, color, 22 minutes (1956). Procurable from The Jacques Holinger Memorial Fund, 700 North Michigan Avenue, Chicago 11, Illinois.

*FOREIGN BODIES IN THE AIR AND FOOD PASSAGES

Paul H. Holinger and Kenneth C. Johnston, Chicago, Illinois

The endoscopic appearance of foreign bodies in the larynx, tracheobronchial tree and esophagus of a series of patients is shown. Fundamental principles of foreign body extraction are illustrated through the removal of various objects from the air and food passages of experimental animals. Silent, color, 25 minutes (1952). Procurable from The Jacques Holinger Memorial Fund, 700 North Michigan Avenue, Chicago 11, Illinois.

*TUBERCULOSIS OF THE LARYNX, BRONCHI AND ESOPHAGUS

Paul H. Holinger and Kenneth C. Johnston, Chicago, Illinois

This film consists of endoscopic photographs of laryngeal, bronchial and esophageal tuberculosis. The laryngeal lesions include those of tuberculous infiltration, more advanced caseous, ulcerating processes, and the final scar tissue deformities associated with healing. The tuberculous lesions in the trachea and bronchi consist of the acute inflammatory stage with obstructing exudate, bronchial deformities associated with collapse therapy and various examples of bronchial stenosis. Esophagoscopic views demonstrate tuberculosis of the esophagus. Silent, color, 13 minutes (1953). Procurable from The Jacques Holinger Memorial Fund, 700 North Michigan Avenue, Chicago 11, Illinois.

*TRACHEOESOPHAGEAL FISTULA

George H. Humphreys II, Columbia-Presbyterian Medical Center, New York, N. Y.

An operative film demonstrating technique of repair of congenital atresia of the esophagus in a newborn infant, including the initial anastomosis of the esophagus and the secondary gastrostomy. Sound, color, 30 minutes (1954). Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut.

*SPONTANEOUS RUPTURE OF THE ESOPHAGUS

S. A. Mackler, Chicago, Illinois

Demonstrates the physiologic mechanism which causes rupture of the esophagus; historical aspects; operative treatment with thoracic approach and surgical repair. Silent, color, 27 minutes (1951). Procurable from author, 1904 South Michigan Avenue, Chicago, Illinois.

TECHNIC FOR REPAIR OF SLIDING AND PARAESOPHAGEAL HIATAL HERNIA

John L. Madden, New York, N. Y.

The surgical repair of two types of esophageal hiatal hernia is shown in some detail. The first case is of the "paraesophageal" type, in which the esophagocardial [illegible] seen on the roentgenogram, is below the diaphragm, and the stomach herniates up throu[illegible] ngside the esophagus. In the more common "sliding" type, which follows, the [illegible] ion is found above the diaphragm. Sound, color, 44 minutes (1957). Procurabl[illegible] Productions, Inc., 322 East 44th Street, New York 17, N. Y.

USE OF THE TRANSVERSE COLON FOR TOTAL ESOPHAGOPLASTY

William E. Neville, Cleveland, Ohio

This film depicts a delayed reconstruction of the esophagus with the colon for a tracheoesophageal fistula with atresia. This one-year-old child had a colon transplanted through his anterior mediastinum to the esophagus in the neck and the stomach. Sound, color, 23 minutes (1955). Procurable from author, 10515 Carnegie Avenue, Cleveland 6, Ohio.

*REPAIR OF DIAPHRAGMATIC HIATUS HERNIA USING FASCIA LATA

J. Norman O'Neill, Queen of Angels Hospital, Los Angeles, California

The transthoracic approach with a demonstration of the technique of opening the chest, isolating esophagus, dissecting of the hernial sac A demonstration of the removal of fascia lata from the thigh, closure of the rent in the diaphragm with fascia lata, closure of the chest with drainage Silent, color, 14 minutes (1952) Procurable from author, 1930 Wilshire Blvd, Los Angeles 57, California

*THE SURGICAL REPAIR OF ATRESIA OF THE ESOPHAGUS WITH TRACHEO-ESOPHAGEAL FISTULA

Willis J. Potts, William L. Riker and Arthur DeBoer. Children's Memorial Hospital, Chicago, Illinois

This film illustrates briefly the essentials of diagnosis and preoperative care of an infant with atresia of the esophagus and tracheo-esophageal fistula The operative procedure is pictured in detail and important steps in the operation are emphasized with drawings Special attention is centered on the importance of postoperative management and feeding Sound, color, 23 minutes (1957) Procurable from American College of Surgeons, 40 East Erie Street, Chicago, Illinois

*GASTROESOPHAGEAL RESECTION FOR CARCINOMA OF THE LOWER ESOPHAGUS

Charles B. Puestow, Veterans Administration Hospital, Hines, Illinois

Motion picture of partial esophagectomy and gastroesophagostomy with emphasis on postoperative care Silent, color, 23 minutes (1953) Procurable from Medical Illustration Department, Veterans Administration Hospital, Hines, Illinois

*EXCISION OF EPIPHRENIC DIVERTICULUM OF THE ESOPHAGUS

Hawley H. Seiler, St Joseph's Hospital, Tampa, Florida

Demonstrates surgical technique involved in removal of large epiphrenic diverticulum of the esophagus X-rays included in the film Silent, color, 12 minutes (1956). Procurable from author, 442 West Lafayette Street, Tampa 6, Florida

*INTRATHORACIC ESOPHAGEAL RECONSTRUCTION WITH RIGHT COLON

Charles D. Sherman, Jr., Earle B. Mahoney, W. Andrew Dale and Samuel J. Stabins, University of Rochester Medical Center, Rochester, N. Y.

The film presents the advantages and disadvantages of other methods of esophageal reconstruction, the indications for esophageal reconstruction, and outlines by semi-animated cut-outs, esophageal reconstruction by retrosternal transplantation of the ileo-colon Operative scenes of its use in an infant with congenital atresia follow Sound, color, 22 minutes (1954) Procurable from Charles D Sherman, Jr, M D, 260 Crittenden Blvd, Rochester 20, N Y

*TRANSTHORACIC REPAIR OF SLIDING HIATAL HERNIA (ALLISON)

William R. Sweetman, Veterans Administration Hospital, Portland, Oregon

This film illustrates the Allison technic for the repair of a sliding hiatal hernia, using the transthoracic and transdiaphragmatic approach The film also contains anatomical drawings which make clear the mechanism of the development of a sliding hiatal hernia, as well as the details of repair Preoperative and postoperative roentgenograms of the patient operated upon are included Silent, color, 20 minutes (1953). Procurable from Central Office Film Library, Veterans Administration Washington 25, D C

*ATRESIA OF THE ESOPHAGUS WITH TRACHEO-ESOPHAGEAL FISTULA

Philip Thorek, Chicago, Illinois

Two cases are presented showing the use of the routine method of anastomosis in one patient, and the use of our own method of anastomosis over a T-tube in the other Both patients are two-day old babies Sound color (1956) Procurable from author, 25 East Washington Street, Chicago 2, Illinois

*CERVICAL DIVERTICULECTOMY (ONE STAGE OPERATION)

Philip Thorek, Chicago, Illinois

Silent, color, 23 minutes (1948) Procurable from author, 25 East Washington Street Chicago 2, Illinois

RESPIRATORY SYSTEM

DIFFERENTIAL DIAGNOSIS AND TREATMENT OF LOBAR EMPHYSEMA OF INFANTS

Osler A. Abbott, Emory University School of Medicine, Emory University, Georgia

This film includes a brief summary of symptoms and signs Comparative films and angiocardiography, a) lobar emphysema and b) unilateral agenesis pulmonary artery Pulmonary findings in resection of left upper lobe with lobar emphysema Demonstration of gross surgical pathology of resected specimen Silent color, 18 minutes (1957) Procurable from author

REPARATIVE SURGERY OF THE TRACHEOBRONCHIAL TREE

Osler A. Abbott, Emory University School of Medicine, Emory University, Georgia

The film shows two aspects of repair, the first being a massive Gebauer graft replacing the lower tracheal wall, carina and medial wall left main stem bronchus for extensive carcinoma, followed by x-ray studies of other applications of such grafts Second, an operation for polyposis of the entire trachea Silent, color, 20 minutes (1956). Procurable from author.

*PNEUMONECTOMY FOR CARCINOMA

William E. Adams, University of Chicago School of Medicine, Chicago, Illinois

This deals with the diagnosis, pathology and surgical technique of total pneumonectomy for primary carcinoma of the lung. The film emphasizes roentgenological diagnosis and pathological characteristics through the use of x-ray studies and special studies of the surgical specimen of five patients with this disease. The surgical technique illustrated includes the operative approach, demonstration of anatomical structures and relations, as well as the pathological lesion encountered. This film ends with Dr. Graham discussing the problem with his first patient, Dr. Gilmore. Sound, color, 35 minutes (1953). Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut.

*COCCIDIOIDOMYCOSIS, ITS EPIDEMIOLOGIC AND CLINICAL ASPECTS

Libero Ajello and Roger Egeberg; directed by Mr. Graham Heid; Public Health Service and Veterans Administration, Washington, D. C.

(See Anatomy, etc.)

*LOBECTOMY, RIGHT UPPER AND MIDDLE LOBES, IN THE TREATMENT OF PULMONARY TUBERCULOSIS

Department of the Army

Demonstrates a lobectomy of the right upper and middle lobes in the treatment of pulmonary tuberculosis. Sound, color, 22 minutes (1951). (See note on page 580 concerning availability of U. S. Army films).

*PHYSIOLOGIC THERAPY IN BRONCHIAL ASTHMA

Alvan L. Barach, Columbia-Presbyterian Medical Center, New York, N. Y.

Effects of pressure breathing, gases and aerosols on patients with severe bronchial asthma. Silent, 12 minutes (1951). Procurable from author, 622 West 168th Street, New York, N. Y.

*IMMOBILIZING LUNG CHAMBER THERAPY IN PULMONARY TUBERCULOSIS

Alvan L. Barach, Columbia-Presbyterian Medical Center, New York, N. Y.

A combined movie illustrating physiologic therapy in bronchial asthma and physiologic and clinical aspects of the use of the immobilizing lung chamber. Silent, 14 minutes (1951). Procurable from author, 622 West 168th Street, New York, N. Y.

*RESUSCITATION FOR CARDIAC ARREST

Claude S. Beck, University Hospitals, Cleveland, Ohio

(See Cardiovascular System).

RECONSTITUTION OF THE LUNG

John W. Bell, Veterans Administration Hospital, Sunmount, N. Y.

The technique of reconstituting the defect remaining after segmental resection in the upper lobe is illustrated in a series of operative scenes. Sound, color, 12 minutes (1956). Procurable from Veterans Administration Central Office, Visual Aids Division, Washington, D. C.

*BRONCHIOGENIC CARCINOMA

Directed by Brian Blades, Washington, D. C. Advisory Committee: William E. Adams and Paul H. Holinger, Chicago, Illinois, John C. Jones, Los Angeles, California, and Alton Ochsner, New Orleans, Louisiana. Produced by Veterans Administration, Washington, D. C.

This film shows that patients with bronchiogenic carcinoma can be cured if diagnosis and treatment are introduced at an early stage of the disease. The incidence of bronchiogenic carcinoma, the diagnostic features and surgical management are presented. Sound, color, 16 minutes (1951). Procurable from United World Films, Inc., 1445 Park Avenue, New York, N. Y.

BRONCHOVASCULAR ANATOMY

William E. Bloomer, A. A. Liebow and M. R. Hales, New Haven, Connecticut

(See Anatomy, etc.)

*NORMAL FLUOROSCOPY OF THE CHEST

Sponsored by the New Jersey Chapter of the American College of Chest Physicians and prepared by Paul K. Bornstein, Asbury Park, and Irving J. Selikoff, Paterson, N. J.

The great increase in the use of fluoroscopy by the general practitioner has been noted by the American College of Chest Physicians. This short film demonstrating routine fluoroscopy technic of the normal chest in various views has been prepared for teaching purposes since there had been no such film available. The film utilizes new technics in fluorophotography, principally, for the first time, the application of the image intensifier. Silent, color, 17 minutes (1955). Procurable from American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

RIGHT TOTAL PNEUMONECTOMY FOR BRONCHOGENIC CARCINOMA

Lyman A. Brewer, III, Los Angeles, California

Sound, color, 22 minutes (1953). Procurable from author, 1930 Wilshire Boulevard, Los Angeles 5, California.

SEGMENTAL RESECTION OF THE LUNG FOR MULTIPLE CONGENITAL ARTFRIOVENOUS ANEURYSMS

O. Theron Clagett, Mayo Clinic, Rochester, Minnesota

The resection of a segment of the upper and lower lobes of the left lung of a 44-year-old man for congenital arteriovenous aneurysms is shown. A hilar dissection is carried out. Vessels leading to the segments of lung containing each aneurysm are dissected out and the segments of lung containing the aneurysms are removed by traction dissection. Silent, color, 12 minutes (1957). Procurable from author or American College of Surgeons, 40 East Erie Street, Chicago, Illinois.

THE ETIOLOGY OF POLLENOSIS

D. Eugene Cowen, Denver, Colorado

This is a film of the primary inhalent (seasonal) flora causing hay fever and asthma with the exception of the so-called "dust" factor, which is so controversial with many men Color, 19 minutes (1953) Procurable from author, 1612 Fremont Place, Denver, Colorado

*DEGENERATIVE LUNG DISEASE

Gerald L. Crenshaw, Oakland, California

This film deals with the patho-physiological state in which the lung vanishes into large air spaces, prior to this, there is a loss of all vascularity so that when the lung is cut at the operating table, while still attached to its blood and air supply, there is no bleeding It also shows the structural damage to the bronchi Sound, 20 minutes (1955) *Procurable from author, 447 Twenty-ninth* Street, Oakland 9, California

*ALLERGY: IMMUNOLOGY, DIAGNOSIS AND TREATMENT

Leo H. Criep, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Part one discusses the essential mechanism of allergy including types of anaphylactic and atopic allergies, production and fixation of antibodies and the antigen-antibody reaction, roles of histamine in allergic phenomenon and the function of antihistamines Part two concerns itself with clinical allergy including illustrative case histories and treatment procedures Sound, color, 45 minutes (1951). Procurable from Nepera Laboratories Division, Yonkers 2, New York

*GLOSSOPHARYNGEAL BREATHING

C. W. Dail and J. Affeldt, Rancho Los Amigos Respiratory Center for Polio, Hondo, California

This film demonstrates the advantages and the technique of glossopharyngeal breathing for patients with severe respiratory muscle paralysis Sound, color, 20 minutes (1954) Procurable from National Foundation for Infantile Paralysis, 120 Broadway, New York, N Y.

*MECHANICAL FACTORS GOVERNING EXPIRATORY OBSTRUCTION TO AIRFLOW

Howard G. Dayman, Chronic Disease Research Institute, University of Buffalo School of Medicine, Buffalo, N. Y.

(See Anatomy, etc.)

*POWER OF POSITIVE PRESSURE

Howard G. Dayman and William Loeser, National Foundation for Infantile Paralysis, Buffalo, N. Y.

Demonstrates the simplicity and effectiveness of positive pressure respiratory aids in patients with chronic respiratory paralysis, for example can permit ambulant program Type of pumps include fireplace bellows Dayman Cough Caddy Sound color, 14 minutes (1956) Procurable from Howard G Dayman, M D, 993 Delaware Avenue Buffalo 9, N Y

*NEW DEVELOPMENTS IN BRONCHOSCOPIC PHOTOGRAPHY AND CINEMATOGRAPHY, INCLUDING ADAPTATION FOR TELEVISION

J. M. Dubois de Montreynaud and R. J. Edwards, Regional Center Against Cancer, Reims, Marne, France.

Demonstration of the equipment (a new French bronchoscope of Fourestier, Gladu and Vulmiere) and demonstration of bronchoscopy with this apparatus Demonstration of television and experimentation in animals Views in color of normal bronchi, tuberculous fistules, malignant tumors *and asthma* Bronchoscopic views in children Sound, color, 25 minutes (1957) *Procurable from* J M Dubois de Montreynaud, M D, 4 rue du General Baratier, Reims Marne, France

*NEW TECHNIC OF BRONCHOSCOPY

J. M. Dubois de Montreynaud, R. J. Edwards and A. J. Gladu, Regional Center Against Cancer, Reims, Marne, France

1) The technic of bronchoscopy with details of equipment, diagrams of the apparatus and of the bronchial tree 2) Tuberculosis—several cases of active fistules and healed fistules 3) Cancers with x-ray and histology 4) Asthma—experimental observations on animals and clinical observations on patients Silent (French-English titles), color 37 minutes (1956). Procurable from J M Dubois de Montreynaud M D, 4 rue du General Baratier, Reims, Marne France

SEGMENTAL RESECTION OF AN ARTERIOVENOUS FISTULA OF THE LUNG

J. L. Ehrenhaft and Montague S. Lawrence, State University of Iowa Hospitals, Iowa City, Iowa

This film was made during resection of pulmonary arteriovenous fistula located in the superior segment of the right lower lobe of the lung Preoperative chest roentgenograms, intravenous angiocardiogram and oxygen saturation studies are presented The arteriovenous pulsations of the fistula are demonstrated prior to segmental resection of the lesion A vinyl plastic injection corrosion cast of the vascular anomaly is also shown Silent, color, 12 minutes (1958) Procurable from author.

*RADICAL PNEUMONECTOMY WITH INTRAPERICARDIAL DISSECTION

F. Henry Ellis, Jr., Mayo Clinic, Rochester, Minnesota

The film portrays the technique used in carrying out intrapericardial dissection at the *time of* pneumonectomy for carcinoma of the lung A typical case is discussed and diagrams of the operative procedure are employed Silent, color, 18 minutes (1955) Procurable from Mayo Clinic, Rochester, Minnesota

*RADICAL PNEUMONECTOMY FOR CARCINOMA

Carmelo Gil-Turner, Grupo Sanatorial de *Santa Marina*, Bilbao, Spain.

This film gathers the technique of radical pneumonectomy for cancer with ligatures within the pericardium and extirpation of all the mediastinal adenopathies in an aged patient Silent, color, 20 minutes (1955) Procurable from author, Clinica F San Sebastian, Rafaela de Ybarra 25, Deusto-Bilbao, Spain

*THE PHYSIOLOGY OF INFANT RESUSCITATION

Roy F. Goddard, Lovelace Clinic, Albuquerque, New Mexico

The mechanical and physical forces influencing neonatal respiration are portrayed in investigative studies of pressure-time relationships and mechanics of breathing studies in the newborn. Intermittent positive pressure resuscitation given with the GBL Infant Hand Resuscitator is demonstrated in the delivery room and the newborn nursery. Sound, color, 15 minutes (1957). Procurable from Lovelace Foundation for Medical Education and Research, 4800 Gibson Blvd., SE, Albuquerque, New Mexico.

*TREATMENT OF RESPIRATORY CONDITIONS IN CHILDREN

Roy F. Goddard, Lovelace Clinic, Albuquerque, New Mexico

The treatment of respiratory conditions in children is portrayed by the investigative work-up of a ten year old girl with asthma and her subsequent treatment with intermittent positive pressure-aerosol therapy. Routine laboratory studies combined with respiratory ventilation studies show her improvement over a period of six months therapy. Sound, color, 13 minutes (1955). Procurable from Lovelace Foundation for Medical Education and Research, 4800 Gibson Blvd., SE, Albuquerque, New Mexico.

PULMONARY RESECTION FOR BRONCHIAL ADENOMA

Alfred Goldman, Beverly Hills, California

Depicts surgery, bronchoscopic, pathology, pre- and post-operative treatment. Silent, color, 24 minutes (1948). Procurable from author, 416 North Bedford Drive, Beverly Hills, California.

EXTRAFASCIAL LUCITE PLOMBAGE FOR PULMONARY TUBERCULOSIS

Alfred Goldman, Beverly Hills, California

Illustrates surgical technic with narration outlining value of this operation in treatment of pulmonary tuberculosis. Sound, color, 24 minutes (1949). Procurable from author, 416 North Bedford Drive, Beverly Hills, California.

*PNEUMONECTOMY FOR BRONCHIECTASIS

Evarts A. Graham, St. Louis, Missouri

This pneumonectomy was performed on a seven year old boy who had universal bronchiectasis of the left lung, dating back for a period of about five years. The surgical plan for this procedure is clearly illustrated and the narration covers the rationale step by step, along with certain precautions that need to be taken. Post-operative x-ray and pictures of the patient are included, six weeks after the procedure. Sound, color, 10 minutes (1950). Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut.

*ECHINOCOCCUS CYST OF THE LUNG; PATHOLOGY AND OPERATIVE REMOVAL

Elliott Harrison, Vancouver, B. C., Canada

Short outline of pathology and epidemiology followed by the operative removal of echinococcus cyst. Silent, color, 10 minutes (1955). Procurable from St. Paul's Hospital, Burrard Street, Vancouver, B. C., Canada.

*ANTI-TUBERCULOSIS DRUGS IN THE MEDICAL AND SURGICAL TREATMENT OF TUBERCULOSIS

H. Corwin Hinshaw and Albert C. Daniels, San Francisco, California

(See Anatomy, etc.)

*A BRONCHOSCOPIC CLINIC IN KODACHROME

Paul H. Holinger, Kenneth C. Johnston and Frank J. Novak III, Chicago, Illinois

This film presents the histories, x-rays, bronchoscopic findings and, where biopsies were taken, the histology, of ten patients with bronchopulmonary disease. The operating room and instrumentarium as well as the technics of anesthesia, of the bronchoscopic examination itself and of the bronchoscopic photography are shown. Silent, color, 30 minutes (1949). Procurable from The Jacques Holinger Memorial Fund, 700 North Michigan Avenue, Chicago 11, Illinois, and the American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

*THE ENDOSCOPIC APPEARANCE OF DISEASES OF THE TRACHEA

Paul H. Holinger and Kenneth C. Johnston, Chicago, Illinois

This film shows congenital stenosis, inflammatory processes and benign and malignant tumors of the trachea as they appear through the tracheoscope and bronchoscope. Silent, color, 20 minutes (1951). Procurable from The Jacques Holinger Memorial Fund, 700 North Michigan Avenue, Chicago 11, Illinois.

*FOREIGN BODIES IN THE AIR AND FOOD PASSAGES

Paul H. Holinger and Kenneth C. Johnston, Chicago, Illinois

(See Esophagus.)

*THE PHYSIOLOGY AND PATHOLOGY OF BRONCHIAL OBSTRUCTION

Paul H. Holinger and Kenneth C. Johnston, Chicago, Illinois

The mechanics of the three stages of bronchial obstruction are demonstrated in this film through the utilization of cinebronchoscopy. The bronchoscopic appearance of bronchial motility responsible for the various degrees of obstruction is shown. Foreign bodies, inflammation and neoplastic disease constitute the obstructing lesions within the bronchi. The roentgen and endoscopic aspects of the problem are correlated throughout the film. Silent, color, 20 minutes (1956). Procurable from The Jacques Holinger Memorial Fund, 700 North Michigan Avenue, Chicago 11, Illinois.

*TUBERCULOSIS OF THE LARYNX, BRONCHI AND ESOPHAGUS

Paul H. Holinger and Kenneth C. Johnston, Chicago, Illinois

(See Esophagus.)

*TRACHEOESOPHAGEAL FISTULA

George H. Humphreys II, Columbia-Presbyterian Medical Center, New York, N. Y.

(See Esophagus.)

*THE BRONCHOPULMONARY SEGMENTS

Chevalier L. Jackson, John F. Huber and Charles M. Norris, Temple University School of Medicine and Hospital, Philadelphia, Pennsylvania

(See Anatomy, etc)

*PERIPHERAL CIRCUMSCRIBED PULMONARY LESION

Harold A. Kipp, Mercy Hospital, Pittsburgh, Pennsylvania

Surgical treatment of circumscribed pulmonary lesion Silent, color, 7 minutes (1955) Procurable from author

*RADICAL SURGERY FOR ADVANCED LUNG CANCER

Adrian Lambert, New York, N. Y.

A film depicting the surgical techniques in the radical approach to advanced lung cancer is shown to demonstrate the correct surgical handling of the chest wall and mediastinum for advanced malignant disease Sound color, 33 minutes (1954) Procurable from Sturgis-Grant Productions Inc, 322 East 44th Street, New York 17, N Y

*TUBERCULOSIS OF THE LARYNX

William A. Lell, Graduate School of Medicine, University of Pennsylvania, Pittsburgh, Pennsylvania

The first part of this film shows various types of laryngeal involvement by tuberculous infection, ranging from minimal inflammatory changes to actual destruction of some of the laryngeal structures The second part deals with a series of cases showing response to streptomycin therapy Silent, color, 25 minutes (1945) Procurable from author, 333 South 18th Street, Philadelphia 3, Pennsylvania

UPPER PARTIAL THORACECTOMY WITH PNEUMOLYSIS (A New Procedure in Surgical Collapse Therapy)

Felipe Margarit, Barcelona, Spain

Operative technic showing resection of 5, 6 and 3 ribs extrapleural pneumolysis through the 3rd periosteal bed resection without periosteal peeling of the 2nd and 1st ribs mediastinal pneumolysis and suture of the intercostal bundles on the apex lung Silent color, 15 minutes (1954) Procurable from author, Calle Balmes 105, Barcelona, Spain

*PRINCIPLES OF RESPIRATORY MECHANICS

Jere Mead, E P. Radford Jr., M. B. McIlroy, B. G. Ferris Jr., and J. L. Whittenberger, Department of Physiology, Harvard Medical School, Boston, Massachusetts

(See Anatomy, etc)

*BCG VACCINATION AGAINST TUBERCULOSIS

National Tuberculosis Association, New York, N Y., and Research Foundation, Chicago, Illinois

(See Anatomy, etc)

SEGMENTAL PULMONARY RESECTION

M. M. Newman, W. F. Lee Jr., and G. A. Coors, U S Naval Hospital, St Albans, New York

Preoperative x-rays technic of resection of apical posterior segmental resection right and left and superior segmental resection left Gross pathology, postoperative x-rays The cases are tuberculous Sound color 35 minutes (1955) Procurable from U S Naval Hospital, Chief of Surgery, St Albans New York

*TREATMENT OF THORACIC INJURIES

Rudolph J. Noer, Louisville, Kentucky

Relates the various types of thoracic injuries to the disturbances in pulmonary function which they produce and demonstrates the principles to be followed in maintaining and/or restoring adequate pulmonary ventilation Sound color 31 minutes (1954) Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut

*RECORDING OXIMETERS AND THEIR APPLICATIONS

John F. Perkins, Jr. and William E. Adams, University of Chicago School of Medicine, Chicago, Illinois

(See Respiratory System)

*LOBECTOMY FOR HYDATID CYSTS OF THE LUNGS

Walter L. Phillips, Cape Town, South Africa

(18 minutes 1949) Procurable from author, Highwick Drive Kenilworth, Cape Town South Africa

*POSTOPERATIVE AEROSEL THERAPY

Max S. Sadove and Ruben C. Balagot, University of Chicago School of Medicine, Chicago, Illinois

Depicts briefly normal and abnormal physiology of respiratory tract, causes of atelectasis, various types of aerosol treatments in postoperative patients and demonstrates the most common types of apparatus and therapeutic agents employed Sound color 25 minutes (1955) Procurable from Winthrop Stearns Inc, 1450 Broadway, New York 18, N Y

*ARTIFICIAL RESPIRATION VIA THE TRACHEOTOMY TUBE

George A. Saxton, Jr., Gareth Gish and Garland Johnson, University of Illinois College of Medicine, Chicago, Illinois

Presentation of various methods of adapting American respiratory equipment to give intermittent positive pressure breathing (IPPB) through an uncuffed tracheotomy tube. Silent, color, 23 minutes (1956). Procurable from George A. Saxton, Jr., M.D., 840 South Wood Street, Chicago 12, Illinois.

REPAIR OF HERNIA OF THE LUNG

L. M. Shefts, San Antonio, Texas

The diagnosis of pulmonary hernia, including roentgenographic findings, is demonstrated. The repairs as shown require dissection and closure of the sac and utilization of periosteal flaps from the ribs above and below the defects. Utilization of wire mesh is also demonstrated. Silent, color, 20 minutes (1952). Procurable from author, 510 Moore Bldg., San Antonio 5, Texas.

PULMONARY DECORTICATION

L. M. Shefts, San Antonio, Texas

The indications for technique and results of pulmonary decortication are demonstrated in cases of unexpandable lungs in tuberculous patients, as follows: Decortication of a tuberculous empyema of six years duration, decortication of a secondarily infected tuberculous empyema of three years duration with contralateral thoracoplasty, and pulmonary decortication followed by contralateral decortication and removal of oleothorax and lower lobe lobectomy. Specimens are shown removed intact as a sac. Silent, color, 35 minutes (1952). Procurable from author, 510 Moore Bldg., San Antonio 5, Texas.

*THE RECOGNITION AND MANAGEMENT OF RESPIRATORY ACIDOSIS

Reginald H. Smart, Hurley L. Motley and Joseph F. Boyle, University of Southern California School of Medicine, Los Angeles, California

(See Anatomy, etc.)

*SPONTANEOUS AND ARTIFICIAL COUGHING PROCEDURES WITH A NEW APPARATUS

Juergen Stoffregen, University Surgical Clinic, Heidelberg, Germany

Spontaneous coughing in a human being after bronchography. Cinematogram of artifically induced coughing in a dog under Pentothal-Na-anesthesia and complete curarization after filling the bronchial tree with different contrast media (Dionosil, Jodipin). Silent, 5 minutes (1956). Procurable from author.

SEGMENTAL PULMONARY RESECTION

John V. Thompson, Methodist Hospital, Indianapolis, Indiana

Film depicts the technique of segmental pulmonary resection and the anatomy in detail. Sound, color, 10 minutes (1956). Procurable from author, 7899 Ridge Road, Indianapolis, Indiana.

*DECORTICATION OF THE UNEXPANDABLE PNEUMOTHORAX LUNG

David H. Waterman, Knoxville, Tennessee

Illustrates technique of operation plus case management. Silent, color, 23 minutes (1950). Procurable from author, 1918 West Clinch Street, Knoxville, Tennessee.

EXTRAPERIOSTEAL LUCITE BALL PLOMBAGE

Francis M. Woods, Overholt Thoracic Clinic, Boston, Massachusetts

The physiological principles which lead to paradoxical motion of the lungs and mediastinum are shown. Their application to thoracoplasty is demonstrated and the use of extraperiosteal plombage to prevent paradoxical motion and make possible a one-stage thoracoplasty is shown. The indications for this procedure are also discussed. Silent, color, 22 minutes (1953). Procurable from author, 135 Francis Street, Boston 15, Massachusetts.

HOSPITAL PERSONNEL

*OCCUPATIONAL THERAPY IN TUBERCULOSIS

Department of the Army

Produced by the U. S. Army in 1949, sound, 27 minutes. (See note on page 580 concerning availability of U. S. Army films.)

*RESUSCITATION FOR CARDIAC ARREST

Claude S. Beck, University Hospitals, Cleveland, Ohio

(See Cardiovascular System.)

*CARDIAC ARREST: IT'S PREVENTION, RECOGNITION AND TREATMENT

Egbert H. Fell and Lowell Peterson, Chicago, Illinois

(See Cardiovascular System.)

*RIGHT HEART CATHETERIZATION

Mr. James Reske and Paul S. Mahoney, University of California School of Medicine, Los Angeles, California

(See Cardiovascular System.)

*CARDIAC ARREST

Henry Swan and J. Cuthbert Owens, Denver, Colorado

(See Cardiovascular System.)

LAITY

*THE AIR WE BREATHE

Mine Safety Appliances Company, Pittsburgh, Pennsylvania

The film is professionally produced, covering the whole field of respirator protection for the worker against dusts, gases and other air contaminants Sound, 26 minutes (1954). Procurable from Mine Safety Appliances Company, Pittsburgh 8, Pennsylvania.

*ARE YOU POSITIVE?

National Tuberculosis Association, New York, N. Y.

An entertaining film in animation and color dealing with prevalent superstitions as well as common misconceptions about tuberculosis Sound, color, 18½ minutes (1957). Procurable from the National Tuberculosis Association, 1790 Broadway, New York, N. Y.

*YOU CAN LICK TB

Veterans Administration, Washington, D. C.

Tells the story of a typical tuberculous patient in a Veterans Administration Hospital. Stresses the importance of rest, readjustment to a less strenuous life, taking interest in the Veterans Administration rehabilitation program in order to become fitted for work within one's physical capacities. Sound, 20 minutes (1950). Procurable from Visual Aids Division, Veterans Administration, Washington 25, D C.

MISCELLANEOUS

TRAUMATIC HERNIA OF THE DIAPHRAGM

William E. Adams, John Todd Reynolds and Peter V. Moulder, University of Chicago and University of Illinois, Chicago, Illinois

This film concerns itself especially with the early diagnosis and effective surgical management of traumatic hernia of the diaphragm A running narration discusses the pertinent clinical features which are usually attendant in these cases and stresses the life saving importance of early attention and effective management X-ray demonstrations are freely used and are combined with pathologic material as well as autopsy specimens to emphasize the above point. Finally, the operative repair of an unusual hernia which projected through the anterolateral aspect of the left diaphragm and out through the left chest wall to lie beneath the skin over that area is demonstrated The surgical principals involved in the management of traumatic hernias of the diaphragm are discussed and illustrated in the operative repair of the above case Emphasis is placed on the frequency of these important lesions and a means of lowering morbidity and mortality when early clinical and roentgenologic features are observed and the possibility of their presence is kept in mind Sound, color, 21 minutes (1957) Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut.

MEDIASTINAL TUMORS

Brian Blades, Washington, D. C.

Sound, color, 39 minutes (1952) Procurable from American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois

*NORMAL FLUOROSCOPY OF THE CHEST

Sponsored by the New Jersey Chapter of the American College of Chest Physicians and prepared by Paul K. Bornstein, Asbury Park, and Irving J. Selikoff, Paterson, N. J.

(See Respiratory System)

*MEDIASTINAL EXPLORATION FOR PARATHYROID ADENOMA

O. Theron Clagett, Mayo Clinic, Rochester, Minnesota

This motion picture illustrates the removal of a parathyroid adenoma from the mediastinum of a patient with hyperparathyroidism The adenoma was located deep in the mediastinum under the arch of the aorta and adjacent to the pulmonary artery. Silent, color, 8 minutes (1955). Procurable from author.

THE SURGICAL CORRECTION OF PECTUS EXCAVATUM

Rollin A. Daniel, Jr., Vanderbilt University School of Medicine, Nashville, Tennessee

The film depicts steps in operation for funnel chest deformity which is a modification of procedure advocated by Doctor Ravitch Color, 9 minutes (1956). Procurable from author, 1211-21st Ave , S , Nashville, Tennessee

*TUMORS OF THE MEDIASTINUM

Carmelo Gil-Turner, Grupo Sanatorial de Santa Marina, Bilbao, Spain

This film shows the resection in all its stages, of a cystic tumor of the mediastinum and the value of the photoradioscopic exploration, since the patient was operated upon when he still presented no symptoms Silent, color, 15 minutes (1955) Procurable from author, Clinica F. San Sebastian, Rafaela de Ybarra 25, Deusto-Bilbao, Spain

*THYMECTOMY FOR MYASTHENIA GRAVIS

Alfred Goldman, Beverly Hills, California

Illustrates the cases of myasthenia gravis with tumor of the thymus and surgical technique for thymectomy. Silent, color, 32 minutes (1950) Procurable from author, 416 North Bedford Drive, Beverly Hills, California.

*EXAMINATION OF THE BREAST

Dudley Jackson, Sr., A. Todd and F. W. Steinberg, Nix Tumor Clinic, San Antonio, Texas

Shows fifteen steps necessary for a breast examination, including technique of expressing breast secretions for early diagnosis of papilloma and intra-mammary pathology Sound, color, 27 minutes (1954) Procurable from Nix Tumor Clinic, 1525 Nix Professional Bldg , San Antonio, Texas

*THORACO-ABDOMINAL NEPHRECTOMY

Robert M. Janes and Charles J. Robson, Toronto, Canada

This film demonstrates the removal of kidney tumors through the abdominothoracic approach. The excellent exposure obtained reduces trauma to the growth, permits early occlusion of the vascular pedicle, and allows complete removal of the neoplasm with the adjacent tissue and lymph nodes. Sound, color, 26 minutes (1955). Procurable from American Cyanamid Company, Surgical Products Division, Danbury, Connecticut.

CHONDROSARCOMA—LEFT COSTAL MARGIN

Frederick E. Kredel and Milton Weinberg, Medical College of South Carolina, Charleston, S. C.

Excision of tumor with lower chest wall and upper abdominal wall. Diaphragm sutured to top of defect. Giant pedicle flap and skin graft for closure. Silent, color, 12 minutes (1954). Procurable from Medical College of South Carolina, Charleston 16, S. C.

*ARE YOU POSITIVE?

National Tuberculosis Association, New York, N. Y.

(See Laity.)

*TREATMENT OF THORACIC INJURIES

Rudolph J. Noer, Louisville, Kentucky

(See Respiratory System.)

*THE HEART CRIPPLER

David S. Ruhe, University of Kansas School of Medicine, Kansas City, Kansas

Kinescope of a TV program on rheumatic fever presented as a part of the series "Highroads to Health," by the University of Kansas. Includes convalescent care and prophylaxis. Narrator: Geoffrey Martin, M.D., Director of Maternal and Child Health, Kansas State Department of Health. Sound, 19 minutes (1957). Procurable from University of Kansas School of Medicine, Kansas City, Kansas.

*EXCISION OF MEDIASTINAL TERATOMA

Hawley H. Seiler, Tampa, Florida

Demonstrates surgical technique involved in removal of extremely large mediastinal teratoma. X-rays and patient also shown on film. Silent, color, 9 minutes (1954). Procurable from author, 442 West Lafayette Street, Tampa 6, Florida.

THORACO—CERVICAL SURGICAL APPROACH TO CARCINOMA OF THE THYROID

Allan Stranahan, John C. McClintock, Ralph D. Alley and Harvey W. Kausel, Albany Hospital and Medical College, Albany, N. Y.

Rationale and demonstration of combined trans-sternal mediastinal and neck dissection with thyroidectomy for carcinoma of the thyroid. Sound, color, 16 minutes (1957). Procurable from Allan Stranahan, M.D., Albany Medical College, Albany, N. Y.

UNITED STATES ARMY MEDICAL MOTION PICTURE FILMS

Send requests to Commanding General, Attention: Surgeon, of the Army Area in which the requesting institution or individual is located:

First U. S. Army, Governors Island, New York
  Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island and Vermont

Second U. S. Army, Fort George G. Meade, Maryland
  Delaware, Kentucky, Maryland, Ohio, Pennsylvania, Virginia and West Virginia

Third U. S. Army, Atlanta 3, Georgia
  Alabama, Florida, Georgia, Mississippi, North Carolina, South Carolina, and Tennessee

Fourth U. S. Army, Fort Sam Houston, Texas
  Arkansas, Louisiana, New Mexico, Oklahoma, and Texas

Fifth U. S. Army, 1660 East Hyde Park Boulevard, Chicago, Illinois
  Colorado, Illinois, Indiana, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Iowa, Wisconsin, South Dakota and Wyoming

Sixth U. S. Army, Presidio of San Francisco, California
  Arizona, California, Idaho, Montana, Nevada, Oregon, Utah and Washington

DISEASES of the CHEST

VOLUME XXXIII JUNE, 1958 NUMBER 6

Studies on the Nature of the Arterial Blood Oxygen Unsaturation in Chronic Pulmonary Disease*,**

HURLEY L. MOTLEY, M.D., F.C.C.P.†

Los Angeles, California

Hypoxemia (anoxemia) occurs when there is interference in the transfer of oxygen from the alveoli to the blood in the capillaries. Hypoxemia may be present although alveolar ventilation is normal. Oxygen diffuses across the pulmonary membrane to combine with hemoglobin (oxyhemoglobin) in the capillaries because there is a difference in partial pressure of oxygen (pO_2) in the two compartments. The oxygen molecules move from a region of higher concentration to a region of lower concentration (diffusion). The pulmonary membrane includes everything through which oxygen must diffuse from the alveolus to combine with the hemoglobin in the red blood cell, namely: alveolar membrane; interstitial fluid between alveolar and capillary membrane; capillary membrane; plasma and outer membrane layer of the red blood cell.

In recent years there has been a revival of studies of measurements of the diffusing capacity of the lung.[1-3] The diffusing capacity of the lung is defined as the quantity of a gas (oxygen or carbon monoxide) transferred each minute for each millimeter of mercury difference in partial pressure of the gas across the alveolar capillary membrane (normal for oxygen greater than 15 at rest). The diffusing capacity is concerned with all factors affecting the diffusion of gases between the alveoli and the pulmonary capillary blood. A decrease in the pulmonary blood flow as a result of a reduced number of patent capillaries or a decrease in the number of capillaries in contact with functioning alveoli decreases diffusion capacity, as well as an increased resistance at the pulmonary membrane for oxygen diffusion. Present tests for diffusion capacity measure the rate of diffusion and local variation with alveolar ventilation and volume (over ventilated alveoli) make difficult the definition and determination of the over-all pulmonary diffusing capacity.

A number of papers have been published in which the term alveolar-capillary membrane block has been used almost synonymously with decreased diffusion capacity of the lung, indicating the defect responsible for unsaturation as being specifically in the alveolar-capillary membrane.

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†From the Cardio-Respiratory Laboratory, University of Southern California School of Medicine.

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Some have assumed that in all cases with fibrosis where emphysema is not a problem and the carbon dioxide is being blown off adequately, that the lowering of the arterial blood oxygen saturation is due to an alveolar-capillary membrane block, and this was even diagnosed from the chest roentgenogram.[4] The term "alveolar-capillary block" has been described as a specific defect in diffusion for oxygen across the pulmonary membrane, where an increased difference between the mean alveolar and mean capillary pO_2 exists, with a resulting lowering in the arterial blood oxygen saturation especially with exercise. Breathing a high oxygen mixture should overcome the block and restore the saturation to normal. Most of the papers reporting measurements on the so-called alveolar-capillary membrane block use 100 per cent oxygen at rest, and if the saturation is 99 to 100 per cent, a diffusion difficulty at the pulmonary membrane is stated to exist. Emphysema and carbon dioxide retention are frequently not present in a significant degree in the presence of severe hypoxia at rest, and more often with exercise, in pulmonary fibrosis, sarcoidosis, the collagen group of diseases and the pneumoconioses. The purpose of this paper is to present data showing that in most cases of pulmonary fibrosis and other pulmonary conditions as listed above, with exception of beryllosis, that the principal cause of the lowering of the arterial blood oxygen saturation is not due to an alveolar-capillary membrane block. The hypoxia is due to perfusion of blood through nonventilated areas especially at the alveolar level and to the presence of poorly ventilated alveoli. The basic consideration in studying the specific cause for unsaturation is based on two simple tests to be described.

Wilson et al[5] report the ratio of the average cross-sectional area involved in diffusion to thickness of the respiratory membranes as 15-31 meters per micron. The surface area of the respiratory alveoli has been estimated, if flattened out, to be from 75 to 100 square meters in man (about the size of a tennis court). By virtue of the large surface area of exposure the passage of the red blood cell through the pulmonary capillaries affords maximal diffusion area for the oxygen to contact the hemoglobin. The thin pulmonary capillaries have been described as virtually hanging in space, thus providing a maximal surface area contact for gas exchange, especially oxygen with the hemoglobin as the red blood cells flow by in single file. The pulmonary bed provides very little tissue support of the capillaries, with most of the gas exchange surface of the vessels exposed to atmospheric pressure. The intimate contact of oxygen and hemoglobin as provided by the alveolar surface area is necessary if all the hemoglobin is to be converted to oxyhemoglobin, for once beyond the capillaries the piling up of red blood cells (4,000,000 to 5,000,000 per cubic millimeter) offers a mechanical barrier to full saturation of all the hemoglobin, even though the oxygen tension of the plasma be adequate or even elevated.

The principle of the large surface area for contact between oxygen and hemoglobin in order to get all of the hemoglobin combined as oxyhemoglobin is employed in measuring oxygen capacity by the Van Slyke method, where a given volume of blood is placed in a proper sized flask, and the flask rotated on the side for 25 minutes (for example, 3 cc. of blood in a 25 cc. Erlenmeyer flask). The thin film of blood affords maximal opportunity for all the hemoglobin to be combined as oxyhemoglobin from the oxygen in the air in the flask. If too much blood be added to a given sized flask (for example, 6 cc. of blood in a 25 cc. flask), the film of blood will be too thick for all of the hemoglobin to be combined as oxyhemoglobin on exposure to air, so that some of the hemoglobin is not converted to oxyhemoglobin by exposure to air in the flask even after 25 minutes (the thickness of the film here being a physical factor impairing the completeness of the reaction). In order for the hemoglobin to be normally oxygenated in the transit through the pulmonary capillary network, the oxygen pressure in the capillary blood (dependent on the alveolar capillary partial pressure of oxygen) must be high while the cells are spread out during passage through the capillaries (time average usually less than 1.0 second).

The measurement of the blood gases in a sample of arterial blood from a systemic vessel such as the brachial artery reflects changes occurring in the lung and in conjunction with analysis of the expired air permits an evaluation of the type of changes which may be present. The saturation of the hemoglobin with oxygen is normally 96 to 98 per cent at sea level on air breathing, both at rest and with exercise, and the slight reduction results from venous admixture in the passage of the blood through the lungs and heart. The normal arterial partial pressure of oxygen (pO_2) is 95 mm. Hg. as measured by direct tension with the Riley[6] bubble method. The mean alveolar pO_2 can be calculated from the arterial pO_2, the arterial pCO_2 and the R.Q. of the expired air. Wilson et al[5] report the normal average oxygen tension in the capillaries as 4 mm. Hg. less than in the pulmonary alveoli, and that 0.01 of the blood flow through the lung normally does not perfuse oxygenating capillaries. For all practical clinical considerations the arterial pCO_2 and the alveolar pCO_2 are the same (CO_2 is about 25 times as diffusible as oxygen in solution). If the arterial blood is unsaturated while breathing air at sea level, the arterial pO_2 is decreased, less than 95 mm. Hg. with a pH of 7.40. The decrease may be due to a lowered oxygen gas tension in the alveoli in all or in part due to inequalities of ventilation. The oxygen tension can be no higher in the blood than in the alveoli perfused as far as known in man, although the possibility of countercurrents as demonstrated in fish gills and swim bladder and in the placenta of many animal species may later be shown to be a factor, especially in conditions with chronically altered hemodynamics and possible extensive collateral circulation between the bronchial and pulmonary vessels. When the mean alveolar pO_2 is normal, a decrease in the arterial blood oxygen saturation as measured from a sample obtained from the brachial artery is due to: (1) a diffusion difficulty at the alveolar-capillary membrane (alveolar-capillary block), (2) shunting of blood through nonventilated areas either in the lung or in the heart, or (3) to poorly ventilated alveoli or nonventilated alveoli.[7]

The blood flow through the lung takes the path of least resistance and apparently selective diversion of the flow of blood occurs in regions with high vascular resistance to areas with less resistance. Many patients with extensive lung disease as revealed by the chest roentgenogram, have surprisingly good arterial blood oxygen saturation at rest, as the blood flow is diverted to the better ventilated and perfused areas. However, with mild exercise gross abnormalities in saturation may be revealed with the increased cardiac output and the loss of the selective diversion of flow. In the evaluation of the blood gas exchange the exercise measurements are frequently of greater importance than the resting measurements.[7] Rest and exercise represent two different hemodynamic situations even in the same individual and studies on both aspects are necessary to obtain the essential information. Some cases, which have 100 per cent saturation at rest on 100 per cent oxygen breathing, will not have 100 per cent saturation if this test were repeated with exercise.

The simple test of using different levels of high oxygen breathing helps to differentiate a true diffusion difficulty (alveolar-capillary membrane block) from shunting at the alveolar level produced by very poorly ventilated alveoli or nonventilated alveoli, whereas 100 per cent oxygen breathing tends to obscure multiple small areas of shunting at the alveolar level because of the very high partial pressure of the dissolved oxygen in the plasma which perfuses ventilated alveoli in the smaller venules before the red blood cells become so piled up as in the larger vessels of a big arteriovenous fistula. A 32 per cent oxygen breathing mixture increases the inspired oxygen tension over 70 mm. Hg., and this is a large enough margin to overcome a diffusion difficulty at the alveolar-capillary membrane if that be the significant or primary difficulty in producing the unsaturation on air breathing. On the other hand, if the decrease in the saturation be due to shunting at the alveolar level, the arterial saturation will not be normal predicted for a 32 per cent oxygen breathing gas, as the increase in the oxygen partial pressure in the plasma will not obscure the shunting at the alveolar level as in the case of 100 per cent oxygen breathing. In some cases even 40 per cent oxygen does not elevate the saturation to the normal level with exercise when the difficulty is due to shunting at the alveolar level. In many cases the arterial blood oxygen saturation is decreased only in a slight to moderate degree at rest, but with mild exercise there is a marked drop in the saturation even though emphysema is not a factor and the maximal breathing capacity is fairly good. Total lung capacity is frequently very markedly decreased in these cases, yet the carbon dioxide may be normal. The decrease in total lung capacity may be due to pulmonary fibrosis, sarcoidosis, asbestosis, collagen type diseases, such as lupus erythematosus and pneumoconiosis.

A second simple test employed in determining the nature of the arterial blood oxygen unsaturation is the use of intermittent positive pressure breathing with compressed air only (no bronchodilators).[8] The intermittent positive pressure breathing (IPPB) produces an increased tidal volume in most cases with some degree of hyperventilation. The increase in mean pressure for the entire breathing cycle is usually less than 5 mm. Hg., when the peak cycling pressure is set at 20 cm. water. If a significant increase in the arterial blood saturation occurs with the pressure breathing on air, the only way to explain this finding is on a basis of providing improved aeration for poorly ventilated alveoli. The pressure breathing at rest on air does not elevate the inspired pO_2 to a sufficient degree to be a factor in overcoming a diffusion difficulty if that be a significant factor present at the alveolar-capillary membrane. Pressure breathing produces no significant change in the resting arterial blood oxygen saturation in cases with proven shunts from right to left in the lung, such as arterio-venous fistula. The improved saturation with pressure breathing on compressed air indicates the presence of poorly ventilated alveoli on ambient air breathing. In some cases an increase was noted in the arterial blood oxygen saturation during mild exercise. This is comparable to that produced by intermittent positive pressure breathing on compressed air only, and represents a more uniform alveolar aeration provided by the deeper breathing with exercise and the increased tidal volume.

Studies of the nitrogen washout employing the nitrogen meter and continuous recording of each breath during 100* per cent oxygen breathing has revealed, especially in severe pulmonary emphysema, marked obstruction at the parenchyma level. In some cases, more than 15 minutes of 100 per cent oxygen breathing are required to reduce the end tidal nitrogen to one per cent, and even then with a forced exhalation, the alveolar

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*The oxygen tanks actually contained 0.3 to 0.5 per cent nitrogen by gas analysis.

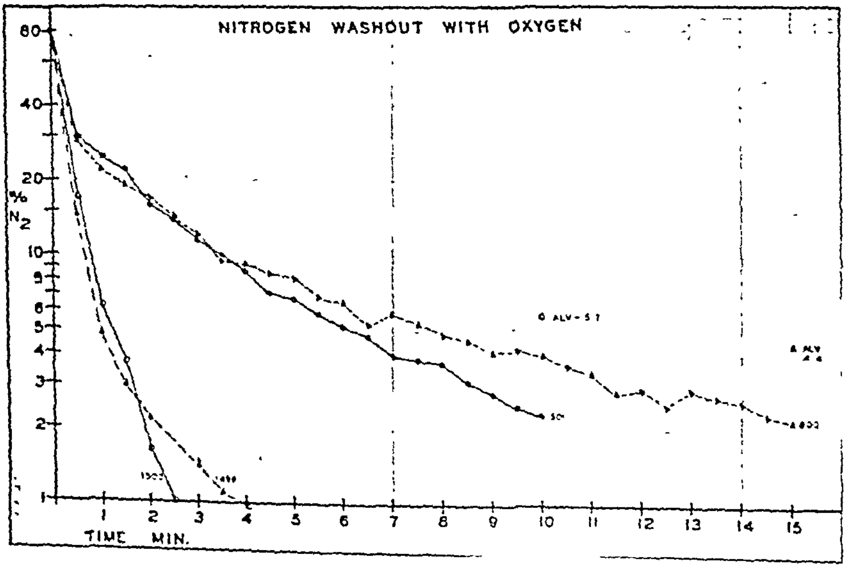

FIGURE 1: Nitrogen washout with oxygen breathing with the Waters Nitrogen Meter in two normals (No. 1500 and No. 1499) and in two patients with severe pulmonary emphysema (No. 1501 and No. 800). In Case 1501 the end tidal nitrogen was 2.3 per cent and the alveolar 5.7 per cent after 10 minutes of oxygen breathing. In Case 800 the end tidal was 2.2 per cent nitrogen with an alveolar of 4.4 per cent nitrogen after 15 minutes of oxygen breathing. This indicates obstruction in the smallest bronchioles in the parenchyma and markedly interferes with the uniformity of alveolar aeration.

TABLE I.—*Studies on the Nature of the Arterial Blood Oxygen Unsaturation in Pulmonary Disease*

Case Number		1	2	3	4	5	6	7	8	9	10	11	12
Diagnosis		Large, AV Fistula, Left Lower Lobe	Multiple, Large A-V Fistula All Lobes	Multiple, Small A-V Fistula All Lobes	Atrial Septal Defect, Pulmonary Hypertension	Bronchiectasis and Emphysema	Fibrosis	Fibrosis	Sarcoidosis	Lupus Erythematosus (?)	Asbestosis	Diatomite Penumoconiosis	Pulmonary Emphysema
Age, years, M (Male) F (Female)		22 (M)	40 (F)	30 (F)	32 (M)	55 (F)	66 (M)	37 (F)	32 (F)	22 (M)	58 (M)	65 (M)	57 (M)
Body Surface Area, Sq. M.		1.69	1.59	1.79	1.70	1.62	1.96	1.59	1.44	1.93	1.60	1.65	1.66
Total Vital Capacity, Per Cent Predicted		79.0	120.3	105.0	66.7	60.8	60.2	47.7	35.6	15.6	69.5	100.0	59.3
Timed Vital Capacity, 3 sec. Per Cent Predicted		79.0	112.1	98.1	58.3	45.9	60.2	47.7	34.2	15.6	56.8	82.8	33.6
Maximal Breathing Capacity, Per Cent Predicted		98.0	123.0	87.1	66.0	63.6	107.3	89.8	75.9	35.4	73.7	95.7	21.5
Residual Air Per Cent Predicted		85.7	116.0	89.6	112.3	158.8	40.6	68.9	57.1	65.0	126.1	132.6	304.9
Total Lung Capacity, Per Cent Predicted		80.0	115.5	98.4	72.3	81.7	55.7	50.0	40.7	24.7	74.1	109.8	120.7
Residual Per Cent Total Lung Capacity		21.0	25.1	18.2	31.1	48.7	21.9	34.5	28.0	52.6	42.5	36.2	63.2
Ventilation Factor, Per Cent		90.2	111.6	98.3	62.9	53.6	95.8	70.0	60.5	29.7	63.1	87.1	31.6
Arterial Blood Oxygen Saturation Per Cent	Rest, Ambient, Air	89.0	64.8	87.6	85.3	92.7	93.8	96.0	87.8	76.1	93.8	92.5	85.2
	Rest, IPPB Air	....	....	87.5	84.5	96.0	96.4	....	92.0	....	96.5	93.5	92.0
	Rest, 32 Per Cent O_2	....	....	....	....	....	....	....	....	95.8	....	....	94.2
	Rest, 40 Per Cent O_2	....	69.0	92.4	86.5	....	....	....	....	....	....	....	....
	Rest, 100 Per Cent O_2	90.6	75.5	97.2	94.4	98.9	99.8	99.0	99.0	99.1	99.6	95.8	97.0

	Exercise, Ambient, Air	86.0	54.8	72.0	54.0	91.8	84.5	83.5	71.6	64.3	82.0	84.8	82.9
	Exercise, IPPB, Air	....	....	....	....	89.2	....	....	....	....	89.5	....	....
	Exercise, 32 Per Cent O_2	....	....	....	....	91.3	89.6	86.8	78.2	....	90.5	90.5	91.7
	Exercise, 40 Per Cent O_2	....	....	....	....	....	....	....	82.5	....	....	....	....
	Exercise, 100 Per Cent O_2	....	64.3	....	63.0	....	93.0	96.0	....	90.0	....	....	....
Arterial CO_2 Content, Volume Per Cent	Rest	39.4	35.1	37.7	37.9	50.8	52.0	44.6	46.0	48.2	45.5	45.1	58.3
	Exercise	38.7	34.2	36.0	42.9	48.1	51.5	41.7	44.5	47.1	45.8	49.3	55.5
Arterial Tensions, Direct Measurement, Rest, mm. Hg.	pCO_2	28.7	29.2	29.0	35.4	57.6	45.1	30.5	46.9	59.1	43.9	34.8	52.1
	pO_2	55.4	43.8	81.3	67.5	75.1	88.9	90.3	66.9	59.5	84.6	88.2	68.9
Alveolar-Arterial pO_2 Difference mm. Hg.		63.0	65.0	32.0	41.7	4.2	4.4	19.6	21.4	4.8	5.8	29.4	14.4
Total Ventilation L./min./sq. M., BSA.	Rest	5.25	6.60	3.87	6.18	2.62	2.72	3.15	3.69	8.36	3.36	4.85	4.50
	Exercise	15.59	13.05	17.00	13.10	8.20	12.07	12.19	12.42	17.14	10.01	17.46	7.19
Oxygen, Uptake, ml./min./sq. M., BSA.	Rest	139	148	123	128	115	102	128	119	156	124	68	102
	Exercise	654	324	508	264	394	443	478	371	259	403	615	248
Oxygen, Per Cent Extracted from Air	Rest	2.65	2.24	3.18	2.07	4.39	3.76	4.06	3.24	1.86	3.69	1.40	2.26
	Exercise	4.19	2.48	2.84	2.08	4.81	3.67	3.92	2.99	1.51	4.02	3.52	3.45
Effective Tidal Air, Rest, Per Cent		77.0	50.5	77.0	50.4	56.0	57.8	85.4	59.0	36.2	63.0	50.4	45.0
Tidal Air, ml.	Rest	739	525	520	498	551	685	542	307	315	376	381	318
	Exercise	1319	988	1039	769	577	986	497	436	329	668	993	477

nitrogen is elevated, Fig. 1. Such severe obstruction markedly impairs the ventilation of many alveoli and results in a lowering of the partial pressure of oxygen in the poorly ventilated alveoli, and in turn the saturation of the hemoglobin in the capillaries perfusing these areas.

The data from the 12 cases presented in Table I illustrate a variety of clinical conditions which show alterations in the arterial blood oxygen saturation both at rest and with exercise (one minute step-up test of 30 steps on an 8-inch stool). Intermittent positive pressure breathing with compressed air only and graded levels of oxygen breathing (32 per cent oxygen and 40 per cent oxygen) as well as 100 per cent oxygen breathing have been compared both at rest and with exercise for the effect on the arterial blood oxygen saturation. A breathing mixture of 32 per cent or 40 per cent oxygen does not obscure shunting at the alveolar level whereas 100 per cent oxygen may obscure shunting at the alveolar level especially at rest. However, with exercise due to alterations in perfusion-ventilation relationships the hemodynamic situation is different from that at rest so that the selective perfusion of blood through the better ventilated areas, which may be present at rest, no longer holds, because the increased cardiac output produces perfusion through more poorly ventilated or nonventilated areas. A 32 per cent oxygen breathing mixture increases the inspired pO_2 over 70 mm. Hg. and this is adequate to more than overcome an alveolar-capillary membrane block which might be present, for if the block were of greater magnitude than this value (alveolar-arterial pO_2 difference of 70 mm. Hg.) the patient would be unable to live on air breathing. The use of a 40 per cent oxygen breathing mixture almost doubles the inspired pO_2 as compared to air breathing. It can be noted that the resting arterial blood oxygen saturation on 100 per cent oxygen in all of the cases except those with large shunts and those with emphysema had a saturation of around 99 per cent or more, Table I. However, the exercise saturation on 100 per cent oxygen may not be normal, even though the saturation is normal at rest. The cases presented in Table I are type cases and illustrate the consistent findings observed in this laboratory in differentiating the nature of the arterial blood oxygen unsaturation. The arterial blood oxygen saturation was determined on the Van Slyke with duplicate checks on two different machines by different technicians. The arterial blood oxygen saturation per cent was also determined on the Water's oximeter double scale cuvette with the use of whole blood. The oximeter was checked daily against the Van Slyke (when properly calibrated, checks consistently within one per cent). Hemoglobin was determined from the flask capacity, direct Van Slyke capacity and the Beckman D-U Model Spectrophotometer using the cyanmethemoglobin method.[10]

In the presence of a large shunt such as an arterial venous fistula in one lobe of the lung (localized in the left lower lobe, by pulmonary angiograms), even 100 per cent oxygen breathing at rest does not produce a normal saturation as shown in Case 1, Table I. In this case there was a very high alveolar-arterial pO_2 difference of 63 mm. Hg. at rest. Ventilation was adequate, emphysema was not a factor, and carbon dioxide was decreased. Studies on this case following a left lower lobe lobectomy revealed the restoration of the normal arterial blood oxygen saturation, 97.5 per cent at rest, 96.3 per cent with exercise and 100 per cent on oxygen breathing. Removal of the large shunt restored to normal the blood gas exchange.

In the presence of multiple large arteriovenous fistulae (pulmonary angiograms showed all lobes involved), the degree of unsaturation was very marked, even on high oxygen breathing mixture, as shown in Case 2 (75.5 per cent at rest on 100 per cent oxygen breathing). The exercise saturation was still lower both with air breathing and on 100 per cent oxygen breathing, Table I. Ventilation was not a factor as alveolar ventilation was increased, and carbon dioxide was blown off at a greater rate than normal as shown by the marked lowering in the arterial CO_2 content and pCO_2 (by direct tension measurements). The alveolar-arterial pO_2 difference was markedly increased 65 mm. Hg. Hyperventilation is a prominent feature in this type of case (a compensatory mechanism to increase as much as possible the arterial pO_2) and decreases the effective tidal air. High oxygen breathing does not correct the saturation to normal at rest in large shunts in the lung of which this is a diagnostic feature.

In the presence of multiple small arterio-venous fistulae in all lobes of the lung, Case 3, the resting saturation on air breathing was considerably higher than noted in the large fistulae in Case 2. The diagnosis in Case 3 was in some doubt not being fully established until after death. Some clinicians doubted the physiological diagnosis of arteriovenous fistula, since (1) pulmonary angiograms were read as negative, (2) a lung biopsy had failed to reveal a fistula and (3) they thought the arterial blood oxygen saturation on oxygen breathing at rest (97.2 per cent) too high for multiple shunts in the lung. Cardiac catheterization revealed a normal pulmonary artery pressure and no evidence of intracardiac shunting from right to left. On 40 per cent oxygen breathing the saturation was only 92.4 per cent, and this can only mean one thing, perfusion of blood through nonventilated areas. An alveolar-capillary membrane block which would produce a 92.4 per cent saturation on 40 per cent oxygen breathing would be inconsistent both with life on air breathing and with the 87.5 per cent saturation obtained on air breathing on rest. The ventilation measurements were good, emphysema was not a factor, and carbon dioxide was decreased as shown by the arterial CO_2 content and pCO_2 by direct tension measurements. Plastic injection of one lung after death revealed multiple small arterio-venous fistulae (actually several mm. in diameter) after the technic of Liebow.[11] Even at the postmortem examination the presence of multiple small arterio-venous fistulae was doubted by the pathologist. The shunting here is at a much smaller level for vessel size as compared to Case 2, but at a much larger level of vessel size (cross section area) as compared to shunting at the alveolar level with vessels smaller than 20 microns in diameter in multiple areas.

Shunting of blood from right to left in the heart reveals similar physiological findings as present in the proven cases of arterio-venous fistulae of the lung. In Case 4 with a proven large atrial septal defect and pulmonary hypertension by cardiac catheterization, the saturation was only 86.5 per cent on 40 per cent oxygen breathing and 94.4 per cent on 100 per cent oxygen breathing at rest. With exercise the saturation was 54.0 per cent on air breathing and on 100 per cent oxygen breathing only 63.0 per cent. The small rise in the saturation occurring with 100 per cent oxygen breathing in conjunction with these other arterial blood saturation findings indicates that with exercise this patient is able to increase only slightly the pulmonary blood flow through the lungs. Most of the blood is simply shunting from right to left with the increased cardiac output of exercise through the septal defect which acts as a safety valve in this case. A marked increase in pulmonary vascular resistance is present and this condition is reflected by the marked decrease in the exercise oxygen uptake on air breathing (264 ml. as compared to the lower limits of normal of 500 ml. of oxygen per minute per square meter, body surface area). These measurements indicate that this patient is an unsatisfactory candidate for septal repair because of the inability to increase the pulmonary blood flow sufficiently above the resting measurements. The septal defect is acting as a safety valve in this case and to close this defect would in all probability precipitate right heart failure.

In bronchiectasis shunting of blood through nonventilated areas has been a very consistent finding especially with exercise. In Case 5 (bronchograms revealed extensive bilateral bronchiectasis) the saturation with exercise was 91.8 per cent on air breathing and even with a high oxygen breathing mixture (32 per cent oxygen) the saturation was not increased. Also intermittent positive pressure breathing on air during step-up exercise did not result in any further increase, actually slightly lower than on ambient air breathing. These figures indicate that the reduced saturation results from the perfusion of blood through nonventilated areas, as the increased inspired pO_2 was over 70 mm. Hg. on the 32.0 per cent oxygen above that on air breathing; yet no increase in saturation resulted. In this patient the resting saturation was increased from 92.7 to 96.0 per cent with intermittent positive pressure breathing on compressed air only, indicating the presence of poorly ventilated alveoli as the primary cause of the reduced saturation at rest. However, with step-up exercise the increase in the saturation did not occur with the intermittent positive pressure breathing on air, indicating that the hemodynamics of rest and exercise are different in the same individual with respect to ventilation perfusion relationships. The saturation was almost normal in this case at rest on 100 per cent oxygen breathing (98.9 per cent). The high oxygen breathing obscures inequalities of distribution at rest, which were demonstrated in this case by the intermittent positive pressure breathing on compressed air only.

In pulmonary fibrosis in the absence of a significant degree of pulmonary emphysema, the most characteristic findings on the ventilatory side consist in the reduced vital capacity and the reduced total lung capacity. Fibrosis results in a restrictive condition of the lung and there may be no bronchospasm. Characteristic findings in pulmonary fibrosis of unknown etiology are illustrated in Cases 6 and 7, Table I. In Case 6 (Fig. 2) the resting saturation was 93.8 per cent, but it was increased to 96.4 per cent (normal) with intermittent positive pressure breathing on compressed air only, demonstrating the presence of poorly ventilated alveoli. The saturation was normal in Case 7 at rest on air breathing. In both cases, 6 and 7, the saturation was normal on 100 per cent oxygen breathing at rest (99 per cent or more). However, in both of these cases with step-up exercise on air breathing there was a marked decrease in the arterial blood oxygen saturation (84.5 per cent in one and 83.5 in the other). The exercise arterial blood oxygen saturation was repeated in both cases using a breathing mixture of 32 per cent oxygen (the inspired pO_2 was increased over 70 mm. Hg.), and in both cases a marked lowering of the arterial blood oxygen saturation was still present, 89.6 per cent in the first case and 86.8 per cent in the second case. The step-up exercise was again repeated using 100 per cent oxygen breathing, and in the first case a saturation of 93 per cent was obtained (a marked lowering for 100 per cent oxygen, and of the magnitude demonstrated in some cases with proven shunts as arterio-venous fistula) and 96 per cent in the second case (a moderate decrease for 100 per cent oxygen). The data obtained with the 32 per cent oxygen and 100 per cent oxygen breathing in these two cases indicates the difficulty producing the marked lowering of the arterial blood oxygen saturation as one of perfusion of blood through nonventilated alveoli with the increased cardiac output with exercise, and these data clearly indicate that the presence of an alveolar capillary membrane block was not a significant factor in these cases. The carbon dioxide is being blown off satisfactorily in both cases as shown by the CO^2 content

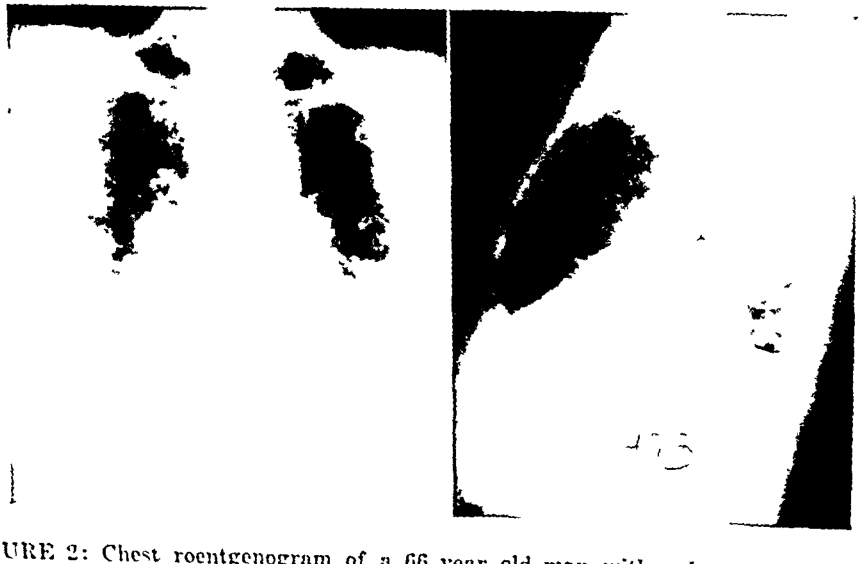

FIGURE 2: Chest roentgenogram of a 66 year old man with pulmonary fibrosis of unknown etiology. The total lung capacity was 56.0 per cent of normal predicted. Residual air was 22 per cent of total lung capacity.

and pCO_2 measurements. The effective tidal air was markedly decreased in the first case indicating the presence of alveoli ventilated but not perfused.

Total lung capacity is frequently markedly decreased in sarcoidosis primarily due to a reduction in the vital capacity and commonly the timed vital capacity is the same as the total indicating the absence of bronchospasm. The residual air may be reduced in similar proportion to the vital capacity. Case 8, Table I (Fig. 3) had typical clinical and x-ray findings of sarcoidosis, and this was further verified by a scalene node biopsy. In this case there was a marked reduction in total lung capacity with a marked reduction in vital capacity without a significant degree of pulmonary emphysema. The resting arterial blood oxygen saturation was quite low (87.8 per cent), and this value was markedly reduced with step-up exercise (71.6 per cent). With intermittent positive pressure breathing on compressed air only there was a significant improvement in the saturation at rest indicating the presence of some poorly ventilated alveoli which could be improved. On 100 per cent oxygen breathing at rest the saturation was normal. In this patient the exercise saturation was determined using both 32.0 per cent oxygen and 40.0 per cent oxygen breathing mixtures, and on 32.0 per cent oxygen the saturation was 78.2 per cent and with 40.0 per cent oxygen the saturation was 82.5 per cent, in both instances demonstrating a very marked decrease due to perfusion of blood through nonventilated areas with the increased cardiac output of exercise. In this case the inspired oxygen tension with exercise was increased far above that necessary to correct a diffusion difficulty of the alveolar-capillary membrane block type, if that had been the significant

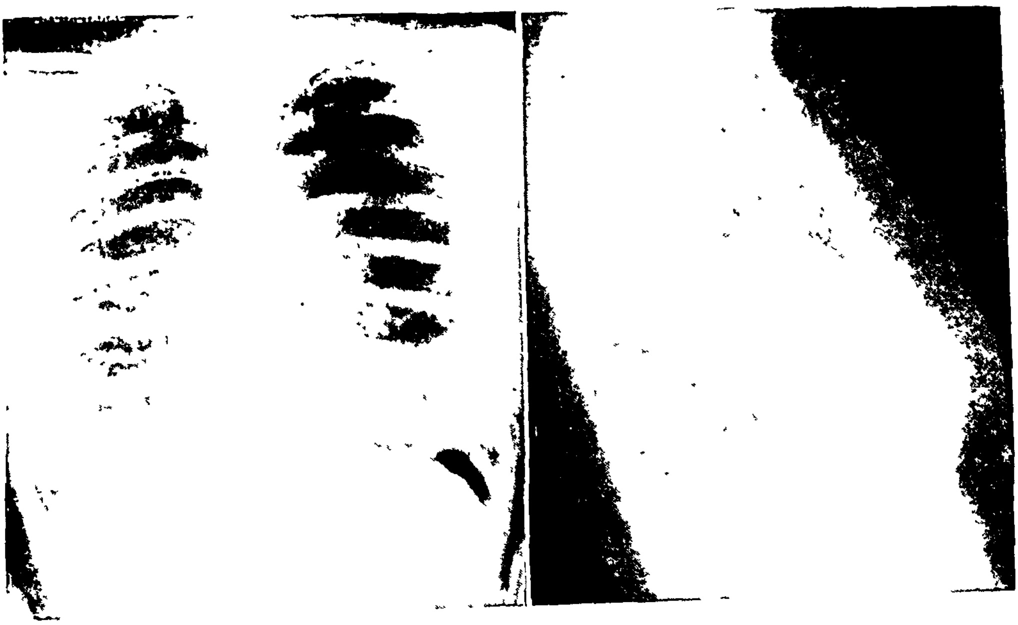

FIGURE 3: Chest roentgenogram of 32 year old woman with sarcoidosis, confirmed by scalene node biopsy. The total lung capacity was 40.7 per cent of normal predicted. Residual air was 28 per cent of total lung capacity.

factor responsible for the reduced saturation. The exercise oxygen uptake in this case was markedly decreased, although the minute ventilation was slightly increased, and this indicates the inability to increase the pulmonary blood flow corresponding to the degree of exercise given and indirectly indicates the presence of increased pulmonary vascular resistance.

Case 9 (Fig. 4) represents a most marked decrease in the total lung capacity (24.7 per cent of normal) due principally to the marked decrease in vital capacity (15.6 per cent of normal). The residual air measurement in this case was only 65.0 per cent of the normal predicted, a moderate to marked decrease; however, with very marked reduction in the total vital capacity, the residual per cent of total lung capacity is markedly increased. The diagnosis in this case has been established with practical certainty as that of lupus erythematosus based on clinical findings and L.E. cell preparation. The resting arterial blood oxygen saturation in this case was very low (76.1 per cent) and even on 32.0 per cent oxygen at rest the saturation was still significantly reduced (95.8 per cent). However, after breathing 100 per cent oxygen the saturation was increased to the normal level. With step-up exercise on air breathing there was a significant further reduction in the arterial blood oxygen saturation as compared to the resting measurement, and the saturation was markedly decreased on 100 per cent oxygen breathing with exercise (90.0 per cent). This case strikingly demonstrates the importance of comparing both rest and exercise on 100 per cent oxygen to conclusively rule out a shunt. The arterial blood oxygen saturation data in this case indicate the shunting of blood through nonventilated or very poorly ventilated areas as the reason for the unsaturation, and not by the presence of an alveolar-capillary membrane block. The exer-

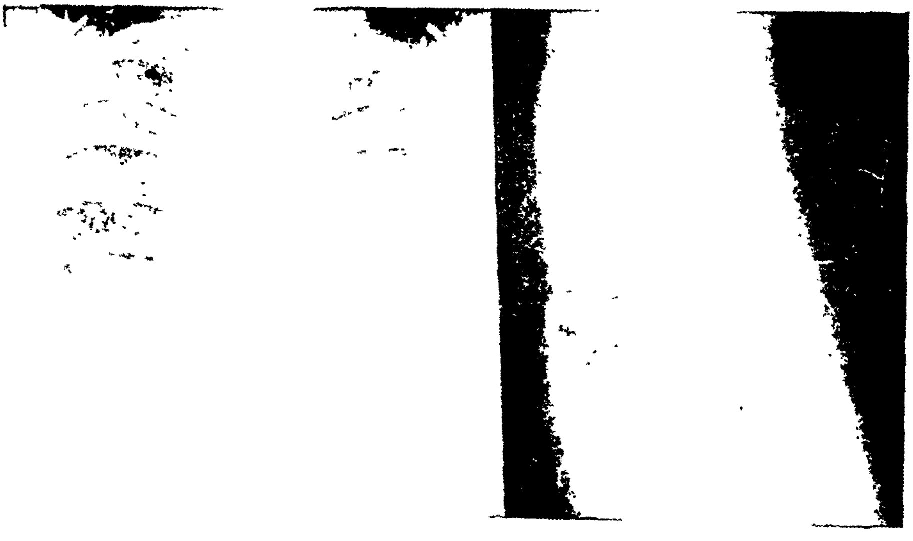

FIGURE 4: Chest roentgenogram of 22 year old man with marked decrease in total lung capacity, 24.7 per cent of normal predicted. The diagnosis has been established with reasonable certainty as lupus erythematosus. The residual air volume was 858 ml. and the vital capacity supine 773 ml.

cise oxygen uptake was markedly decreased in this case indicating the presence of increased pulmonary vascular resistance. The effective tidal air was also markedly decreased indicating the ventilation of many areas in the lung, which were not perfused. The marked reduction in the average tidal volume accounts for part of the decreased effective tidal air because of increased dead space ventilation.

Asbestosis is frequently accompanied by a significant reduction in total lung capacity, a restrictive condition with or without the presence of a significant degree of pulmonary emphysema or bronchospasm. Case 10 (Fig. 5) was an asbestosis worker of 37 years exposure with typical x-ray findings of asbestosis. There was a moderate decrease in total lung capacity accompanied by a moderate increase in the absolute value of the residual air and a moderate degree of pulmonary emphysema. The resting arterial blood oxygen saturation was decreased from 93.8 per cent at rest to 82.0 per cent with step-up exercise, a very marked decrease. The saturation was normal (99.6 per cent on 100 per cent oxygen breathing at rest). However, the saturation was markedly decreased with step up exercise (90.5 per cent) on a high oxygen breathing mixture (32.0 per cent oxygen). With intermittent positive pressure breathing on compressed air only during step-up exercise the saturation was increased almost as much as with the 32.0 per cent oxygen breathing mixture (89.5 per cent as compared to 90.5 per cent). The exercise arterial blood oxygen saturation data in this case indicate the decrease due to perfusion of blood through nonventilated or poorly ventilated alveoli, and not due to an alveolar-capillary membrane block. Carbon dioxide was blown off adequately both at rest and with exercise.

Case 11 is that of a diatomite worker with a history of 35 years exposure to diatomaceous earth. The x-ray film revealed changes consistent with the presence of diatomite pneumoconiosis with conglomerate changes. The lung volume measurements revealed a moderate increase in the

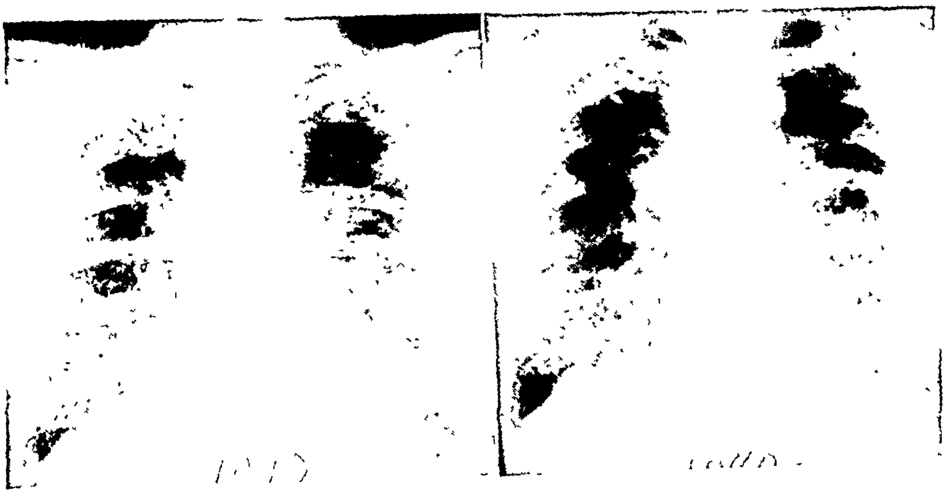

FIGURE 5: Chest roentgenogram of 58 year old man with a history of working in asbestos plant for 37 years. The vital capacity is markedly decreased without obstruction, and total lung capacity is moderately decreased.

absolute value of the residual air and a moderate degree of pulmonary emphysema. The arterial blood oxygen saturation was decreased from 92.5 per cent at rest to 84.8 per cent with step-up exercise, a marked decrease. The resting saturation was not significantly increased with intermittent positive pressure breathing in this case. The resting saturation on 100 per cent oxygen was markedly decreased, indicating extensive perfusion of blood through nonventilated areas even at rest. The exercise saturation on 32.0 per cent oxygen was markedly decreased (90.5 per cent) indicating extensive perfusion of blood through nonventilated areas. The carbon dioxide content and tension were decreased slightly at rest due to hyperventilation. The elevated alveolar-arterial pO_2 difference was due partly to the hyperventilation with the elevated mean alveolar pO_2. Hyperventilation was quite marked with exercise and the lung ventilation efficiency was markedly decreased as shown by the reduced per cent of oxygen extracted and the decreased effective tidal air.

Pulmonary emphysema of a severe degree is characterized by an increased residual air, a decreased timed vital capacity and maximal breathing capacity, a decreased arterial blood oxygen saturation especially with exercise, an elevated CO_2 content in most cases, a decreased exercise oxygen uptake, and a decreased per cent of the effective tidal air.[12] Case 12 in Table I is typical of severe pulmonary emphysema and demonstrates the above findings. The ability to use the chest and lungs as a bellows is markedly impaired as shown by the ventilation factor at 31.6 per cent. A severe degree of hypoxia was present at rest, and this was increased slightly with exercise. Intermittent positive pressure breathing on compressed air only resulted in an increase of 6.8 per cent in the resting arterial blood oxygen saturation, a significant figure and demonstrating the presence of many poorly ventilated alveoli, a finding so characteristic of pulmonary emphysema. In this case the saturation was only 94.2 per cent on the 32.0 per cent oxygen breathing mixture indicating not only the presence of poorly ventilated alveoli, but also a significant amount of perfusion of blood through nonventilated alveoli even at rest. The saturation was also decreased on 100.0 per cent oxygen breathing at rest, 97.0 per cent (normal 99.0 per cent or more). With step-up exercise on the 32.0 per cent oxygen breathing mixture, the saturation was markedly decreased, 91.7 per cent, indicating extensive perfusion of blood through nonventilated areas and that an alveolar-capillary membrane block was not a significant factor in this case. The carbon dioxide was significantly elevated in this case both at rest and with exercise. The exercise oxygen uptake is markedly decreased, indicating a marked increase in pulmonary vascular resistance and the inability to increase the cardiac output very much above the resting level. The effective tidal air was only 45 per cent indicating the presence of many alveoli which were ventilated but not perfused.

Discussion

If the lowering of the arterial blood oxygen saturation with exercise results from a diffusion difficulty of the alveolar-capillary membrane, then the high oxygen breathing mixture (32.0 per cent oxygen) with the resulting increased inspired pO_2 (over 70 mm. Hg.) should restore the blood saturation to a normal level of 97 per cent or more. Pulmonary emphysema and fibrosis cases in general with hypoxia on air breathing do not show a normal exercise saturation of 97.0 per cent or more on a high oxygen breathing mixture, such as 32.0 per cent, or in many cases even 40.0 per cent. The data indicate that during step-up exercise with the increased cardiac output from the right side of the heart, some blood bypasses ventilated alveoli with shunting at the alveolar level, a condition in which the use of graded level of high oxygen breathing mixtures (32.0 per cent or 40.0 per cent oxygen) does not correct. Even 100 per cent oxygen breathing does not elevate the saturation to the normal level of 99 per cent or more in all cases of severe pulmonary insufficiency. In pulmonary fibrosis and emphysema in general, the lowering of the arterial blood oxygen saturation which occurs at rest and with exercise results from alteration in the ventilation-perfusion relationship. Some alveoli are poorly aerated, yet perfused either normally or with a decreased amount of blood, other alveoli are perfused but not aerated (this latter condition represents a small shunt at the alveolar level), and some alveoli are ventilated but not perfused with blood. Furthermore, 100 per cent oxygen breathing due to the very high increase in the partial pressure of oxygen in the plasma which perfuses ventilated alveoli will tend to obscure shunting or the venous admixture at the alveolar level, whereas 32.0 per cent oxygen or 40.0 per cent oxygen breathing will not obscure the shunting at the alveolar level, yet the oxygen tension in the alveoli will be more than enough to overcome an alveolar capillary-membrane block if present on air breathing (if the block be a significant factor in producing the unsaturation).

SUMMARY

1. Our studies indicate that shunting producing arterial blood oxygen unsaturation is one of varying magnitude whether it be due to an arterio-venous fistula of the lung, intracardiac shunting from right to left or at the alveolar level in chronic pulmonary diseases such as: pulmonary fibrosis, collagen diseases, sarcoidosis, pneumoconiosis and emphysema. The decrease noted in the arterial blood oxygen saturation with exercise on air breathing was not restored to a normal level on a high oxygen breathing mixture (such as 32.0 per cent oxygen) as one would expect if the major difficulty were alveolar capillary-membrane block.

2. The use of (1) graded levels of oxygen breathing, especially 32.0 per cent oxygen and 40.0 per cent oxygen, and (2) the use of intermittent positive pressure breathing on compressed air only constitute simple tests indicating the nature of the arterial blood oxygen unsaturation.

3. The use of 100 per cent oxygen breathing at rest in an inadequate test to rule out shunting, as this not only obscures shunting at the alveolar level, but in some cases if measured with exercise a decreased saturation results in the presence of a normal resting saturation (100 per cent).

4. These studies indicate that in chronic pulmonary disease in general (except beryllosis) that the primary cause of the arterial blood oxygen unsaturation is due to the presence of poorly ventilated alveoli or to the perfusion of blood through nonventilated or poorly ventilated areas and that an alveolar-capillary membrane block is not a significant factor producing the hypoxia.

RESUMEN

1. Nuestros estudios indican que al intercomunicación que produce deficiente saturación de oxígeno en la sangre arterial es de variable magnitud ya sea que se deba a una fístula arteriovenosa en el pulmón, intercomunicación intracardiaca de derecha a izquierda, o que se establezca el nivel alveolar en enfermedades crónicas tales como: fibrosis pulmonar, enfermedades colágenas, sarcoidosis, neumoconiosis, y enfisema.

El decrecimiento observado en la saturación de la sangre arterial después del ejercicio al respirar aire, no se restauró a lo normal usando una mezcla elevada de oxígeno (tal como 32.0 por ciento de oxígeno) como uno podría esperar si la dificultad mayor fuese el bloqueo de la membrana alveolocapilar.

2. El uso de (1) niveles graduales de oxígeno inhalado, especialmente de 32 por ciento de oxígeno y 40 por ciento de oxígeno y, (2) el uso de la respiración a presión positiva intermitente con sólo aire comprimido constituyen pruebas simples que indican la naturaleza de la insaturación sanguínea arterial.

3. El uso de oxígeno al 100 por ciento respirado en reposo es un medio inadecuado para descubrir la intercomunicación puesto que esto no sólo obscurece la intercomunicación al nivel de los alveolos sino que en algunos casos, si se mide en ejercicio, resulta una saturación disminuida en presencia de una saturación normal en reposo (100 por ciento).

4. Estos estudios demuestran que en las enfermedades pulmonares crónicas en general (con excepción de la beriliosis) la causa primaria de la insaturación arterial es la existencia de alveolas mal ventilados o la perfusión de la sangre a través de no ventilados o mal ventilados y que el bloqueo de una membrana alveolocapilar no es un factor de significación para producir hipoxia.

RESUME

1. Nos études indiquent que le shunt, ne permettant pas la saturation de l'oxygène artériel est d'importance variable selon qu'il est dû à une fistule artério-veineuse du poumon, à un shunt intra-cardiaque de droite à gauche, ou au niveau des alvéoles dans les affections chroniques du poumon, les affections étant la sclérose pulmonaire, les maladies du collagène, la sarcoidose, les pneumoconioses, et l'emphysème. La diminution de la saturation oxygénée artérielle, après exercices respiratoires, ne peut pas être ramenée à un niveau normal par la respiration d'un mélange à haute teneur d'oxygène (tel que 32%). Tout se passe comme si l'obstacle essentiel était une obstruction de la membrane alvéolo-capillaire.

2. L'emploi de 1) taux calculés d'oxygène, particulièrement 32% et 40%; et de 2) une respiration en pression positive intermittente, sous air

comprimé, ne constituent que des tests simples qui ne permettent de connaitre que la nature de la désaturation artérielle oxygénée.

3. L'emploi de la respiration oxygénée à 100% au repos est un test impropre à juguler le shunt, parce que non seulement ainsi est masqué le shunt au niveau de l'alvéole mais dans certains cas, il donne une saturation diminuée si la mesure est faite en cours d'exercice tandis que la saturation est normale au repos.

4. Ces études montrent que dans les affections pulmonaires chroniques (bérylliose exceptée) la cause *primaire de la non-saturation* artérielle oxygénée est due à la présence d'alvéoles faiblement ventilées ou à la perfusion de sang à travers des zones non ventilées ou faiblement ventilées et que l'obstruction de la membrane alvéolo-capillaire n'est pas un facteur important d'hypoxémie.

ZUSAMMENFASSUNG

1. Unsere Untersuchungen weisen darauf hin, dass eine einen shunt bildende arterielle Blutsauerstoff-Untersättigung in ihrem Ausmass wechselt, je nach dem, ob sie die Folge einer arterio-venösen Fistel der Lunge ist, einem intracardialen Redhts-Links-shunt, oder auf der Höhe der Alveolen bei chronischen Lungenkrankheiten, wie Lungenfibrose, Bindegewebserkrankungen, Sarkoid, Pneumokoniose und Emphysem. Der Abfall in dearteriellen Blutsauerstoff-Sättigung bei Belastung unter Luftatmung wurde nicht wieder bis auf einem normalen Wert gebracht durch ein Sauerstoffhaltiges Atemgemisch (wie z.B. 32% Sauerstoff), wie man dies erwarten konnte, wenn das Haupthindernis in einem alveolaerem Kapilarblock bestünde.

2. Die Benutzung von (1) abgestuften Mengen von Sauerstoffatmung, besonders 32% Sauerstoff und 40% Sauerstoff, und (2) die Benutzung intermitierender positiver Druckatmung unter komprimierter Luft stellen nur einfache Testverfahren dar, die die Natur der arteriellen Blutsauerstoff-Untersättigung anzeigen.

3. Die Benutzung einer Sauerstoffatmung von 100% bei Ruhe ist ein nicht adaequater Test zum Ausschluss eines shunt, weil des Verfahren nicht nur den shunt in Höhe der Alveolen verbirgt, sondern in manchen Fällen bei Messung unter Belastung in Gegenwart einer normalem Ruhesättigung (100%) zu einer verminderten Sättigung führt.

4. Diese Untersuchungen weisen darauf hin, dass im allgemeinen bei chronischer Lungenerkrankung (ausgenommen Berrylosis) die Hauptursache der mangelhaften arteriellen Blutsauerstoffsättigung die Folge des Vorliegens schwach beatmeter Alveolen ist oder der Blutströmung durch nicht ventilierte oder schwach ventilierte Bezirke und dass ein alveolärer Kapilar-Membran-Block kein signifikanter Faktor ist für das Zustandekommen der Hypoxie.

REFERENCES

1 Riley, R. L., Cournand, A. and Donald, K. W.: "Analysis of Factors Affecting Partial Pressures of Oxygen and Carbon Dioxide in Gas and Blood of Lungs: Methods," *J. Applied Physiol.*, 4:102, 1951.

2 Filley, G. F., MacIntosh, D. J. and Wright, G. W.: "Carbon Monoxide Uptake and Pulmonary Diffusing Capacity in Normal Subjects at Rest and During Exercise," *J. Clin. Invest.*, 33:530, 1954.

3 Forster, R. E., Fowler, W. S. and Bates, D. V.: "Considerations on the Uptake of Carbon Monoxide by the Lungs," *J. Clin. Invest.*, 33:1128, 1954.

4 Marks, A., Cugell, D. W., Cadigan, J. B. and Gaensler, E. A.: "Clinical Determination of the Diffusion Capacity of the Lungs, Comparison of Methods in Normal Subjects and Patients with 'Alveolar-Capillary Block' Syndrome," *Am. J. Med.*, 22:51, 1957.

5 Wilson, R. H., Evans, R. L., Johnson, R. S. and Dempsey, M. E.: "An Estimation of the Effective Alveolar Respiratory Surface and Other Pulmonary Properties in Normal Persons," *Am. Rev. Tuberc.*, 70:296, 1954.

6 Riley, R. L., Proemmel, D. D. and Franke, R. E.: "A Direct Method for Determination of Oxygen and Carbon Dioxide Tensions in Blood," *J. Biol. Chem.* 161:621, 1945.

7 Motley, H. L.: "Pulmonary Emphysema, Cardio-Respiratory Disturbance," *Dis. Chest*, 29:292, 1956.

8 Motley, H. L. and Tomashefski, J. F.: "Effect of High and Low Oxygen Levels and Intermittent Positive Pressure Breathing on Oxygen Transport in the Lungs in Pulmonary Fibrosis and Emphysema," *J. Applied Physiol.*, 3:189, 1950.

9 Motley, H. L., Smart, R. H. and Valero, A.: "Pulmonary Function Studies in Diatomaceous Earth Workers, (1) Ventilatory and Blood Gas Exchange Disturbance," *Arch. Indust. Health*, 13:265, 1956.

10 Evelyn, K. A. and Malloy, H. T.: "Microdetermination of Oxyhemoglobin, Methemoglobin and Sulfhemoglobin in a Single Sample of Blood," *J. Biol. Chem.*, 126:655, 1938.

11 Liebow, A. A., Hales, M. R., Lindskog, G. E. and Bloomer, W. E.: "Plastic Demonstrations of Pulmonary Pathology," *J. Tech. Methods*, 27:116, 1947.

12 Motley, H. L. and Smart, R. H.: "Pulmonary Emphysema: Physiological Factors in Diagnosis and Advances in Therapy," *J. Am. Geriatrics Soc.*, 3:316, 1955.

Comparison of 4,4′-Diaminodiphenylsulfone and Its Thymolated Derivative in Experimental Tuberculosis in Guinea Pigs

ALFRED G. KARLSON, D.V.M., PH.D.
Rochester, Minnesota

Although 4,4′-diaminodiphenylsulfone (DDS) has definite antituberculosis effects in guinea pigs infected with the human type of tubercle bacilli,[1] the toxicity of this drug has precluded its acceptance in the treatment of tuberculosis in humans. DDS and a few of its derivatives are widely used in leprosy because no other equally effective agents are available for the treatment of this disease; however, the toxicity of these drugs also limits their usefulness in this disease.[2] Consequently, a large number of derivatives of DDS have been prepared and studied in an effort to obtain a relatively nontoxic but active antimycobacterial drug. The evidence indicates that most of these derivatives may have no advantage over DDS itself.[3-5]

Of current interest is a derivative of DDS that is said to be relatively nontoxic. It is 4,4′-bis (6-thymylazo)-diphenylsulfone, which is derived from DDS by diazotization and coupling with thymol (Fig. 1). This drug will be referred to as DDS-thymol.

Therapeutic trials with DDS-thymol in tuberculous patients who failed to respond to other treatment indicated that the drug had beneficial effects and was nontoxic.[6,7] It is reported to be nontoxic for guinea pigs,[8] which is in contrast to the well known hematotoxic effect in guinea pigs of DDS and some of its derivatives.[5]

DDS-thymol had no therapeutic activity in experimental tuberculosis in mice.[9] In tuberculous guinea pigs, however, the daily administration of 400 mg. of DDS-thymol increased the survival time and promoted healing of the ulcer at the site of inoculation. Also, fewer acid-fast bacilli were present in smears of various organs in comparison to the findings in untreated animals.[10]

The following report describes a study in which it was found that administration of DDS-thymol to tuberculous guinea pigs resulted in regression and healing of lesions as determined by gross and histopathologic examination. This compound appeared to be less effective than DDS but it was less toxic.

Methods

Each of 36 mature male guinea pigs, weighing approximately 600 gm. apiece, received an intraperitoneal injection of 0.1 mg. (moist weight) of virulent human-type tubercle bacilli (H37Rv). On the 16th day after infection, six animals were killed to obtain evidence that a progressive disease had been established; these six animals were the pretreatment

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Section of Bacteriology, Mayo Clinic and Mayo Foundation.
The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

controls. On the same day, the remaining 30 animals were divided into three groups of 10 animals each as follows: (1) controls; (2) those treated with DDS,* 0.5 per cent in the diet; (3) those treated with DDS-thymol,* 1.0 per cent in the diet. All animals were fed Purina rabbit chow** to which was added 0.1 per cent of abscorbic acid.

The drugs (in powdered form) were mixed daily with the diet. The amount of DDS-thymol was selected somewhat arbitrarily. A preliminary trial showed that normal guinea pigs continued to gain weight when fed a diet containing 1.0 per cent of DDS-thymol. The amount of DDS was selected on the basis of unpublished observations showing that a diet containing 0.5 per cent of DDS, although hematotoxic, had a great therapeutic effect on tuberculosis in guinea pigs.

Six of the control animals had died by the 131st day of infection, and three of the four remaining controls were losing weight. Therefore, the experiment was discontinued on the 132nd day of infection (116 days of treatment). All surviving animals were killed. The lesions seen at necropsy were recorded schematically as shown in Figure 2. Suitable portions of tissue were preserved for histopathologic examination.

Results

Mortality.—As already indicated, six of the control animals had died by the 131st day of infection (Fig. 2). Of those given DDS-thymol, two died after only 3 and 20 days of treatment, respectively, and were considered as failures. Two other animals in this group died after 53 and 81 days of treatment, respectively. No deaths occurred in the group treated with DDS.

Gross and Histopathologic Observations.—The animals killed on the 16th day of infection (pretreatment controls) had visible lesions in the liver and spleen (Fig. 2); small tuberculous foci were seen microscopically in the lungs. It is presumed that the disease in the remaining animals, when the treatment period started, was comparable to that in the pretreatment controls. The lesions in the control animals were typical of the widespread destructive tuberculous process usually seen in experimentally infected guinea pigs.

In the group treated with DDS-thymol, the two animals considered as failures had lesions similar to those of the controls, as did also the two animals which died after 53 and 81 days of treatment. Of the six animals which received treatment for the entire 116-day period, one had a few visible lesions in the liver. This animal, as well as two others, had small but active microscopic caseous foci in the lungs. Aside from this, sections of lungs, liver and spleen of the animals given DDS-thymol contained no other microscopic evidence of actively progressing tuberculous foci. However, caseous lesions were present in the tracheobronchial, hepatic and iliac lymph nodes of each animal.

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*The DDS and DDS-thymol were obtained from Dr. E. F. Roberts, Wyeth Laboratories, Philadelphia, Pennsylvania.

**Purina rabbit chow is manufactured by the Ralston Purina Company, St. Louis, Missouri.

Of the animals treated with DDS, two had multiple miliary lesions in the lungs visible at necropsy and two others had small caseous pulmonary lesions demonstrable microscopically. Peculiarly, active lesions were not seen in sections of liver or spleen of the four animals with pulmonary lesions. Sections of lungs, liver and spleen of the other animals in this group were free of active tuberculous disease. However, caseous foci were present in the tracheobronchial, hepatic and iliac lymph nodes of all the animals treated with DDS.

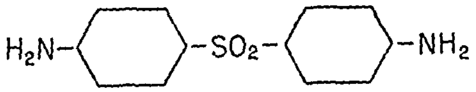
The index of infection, based on the extent and character of the lesions as determined histopathologically,[11] was as follows: pretreatment controls, 55; controls, 90; those receiving DDS-thymol, 1.0 per cent in the diet, 30.0; those receiving DDS, 0.5 per cent in the diet, 15.0. The index for the animals treated with DDS-thymol includes the two which died after 53 and 81 days of treatment. If these are excluded, an index of 20 was determined for the six animals treated during the entire 116-day period.

Toxicity.—Although this study was made primarily to determine the therapeutic effect of DDS-thymol, certain limited observations suggest that this drug was well tolerated. The animals gained weight during the period of treatment. Sections of kidneys, lungs, liver and spleen showed no morbid changes that could be attributed to the drug.

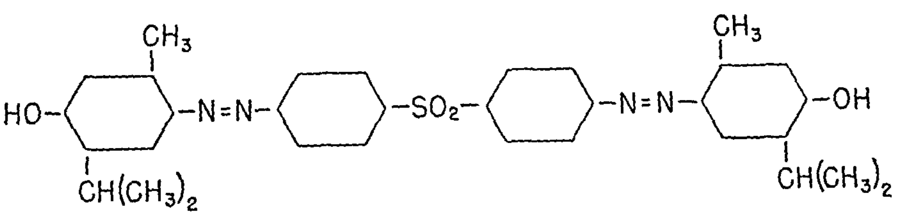
The hematotoxic effects of DDS were manifested by the enlargement and the deep-purple color of the spleens of all animals in this group. Microscopically, the splenic sinusoids were greatly distended. Numerous pigment-laden macrophages lined the sinusoids and also were situated within the splenic cords. This pronounced change in the structure of the spleen was not seen in the animals given DDS-thymol.

Comment

These results show that the administration of DDS-thymol to tuberculous guinea pigs resulted in regression of the disease but give no indication



4,4′-diaminodiphenylsulfone



4,4′-bis(6-thymylazo)-diphenylsulfone

FIGURE 1: Structural formula of 4,4′-bis (6-thymylazo)-diphenylsulfone (molecular weight 570.7) compared to that of 4-4′-diaminodiphenylsulfone (molecular weight 248.3).

of the mode of action of the drug. There is a question as to whether DDS-thymol acts directly or owes its effect to the liberation of DDS. According to Rist and associates,[9] 90 per cent of the DDS-thymol given orally to mice is eliminated in the feces, which accounts for its inactivity against tuberculosis in this species. These workers considered that the reported low toxicity of DDS-thymol is due to the fact that it is stable and releases only small amounts of DDS in vivo. Furthermore, Rist's group ascribed the reported beneficial effects of DDS-thymol in tuberculosis and leprosy to liberation of small amounts of DDS over a prolonged period of therapy. In guinea pigs, on the other hand, Cotereau and associates[12, 13] reported that DDS-thymol is absorbed and is present in the blood in concentrations as much as 20 times those of the DDS which is liberated. These workers thought that DDS-thymol acts directly and does not owe its effect to the release of DDS.

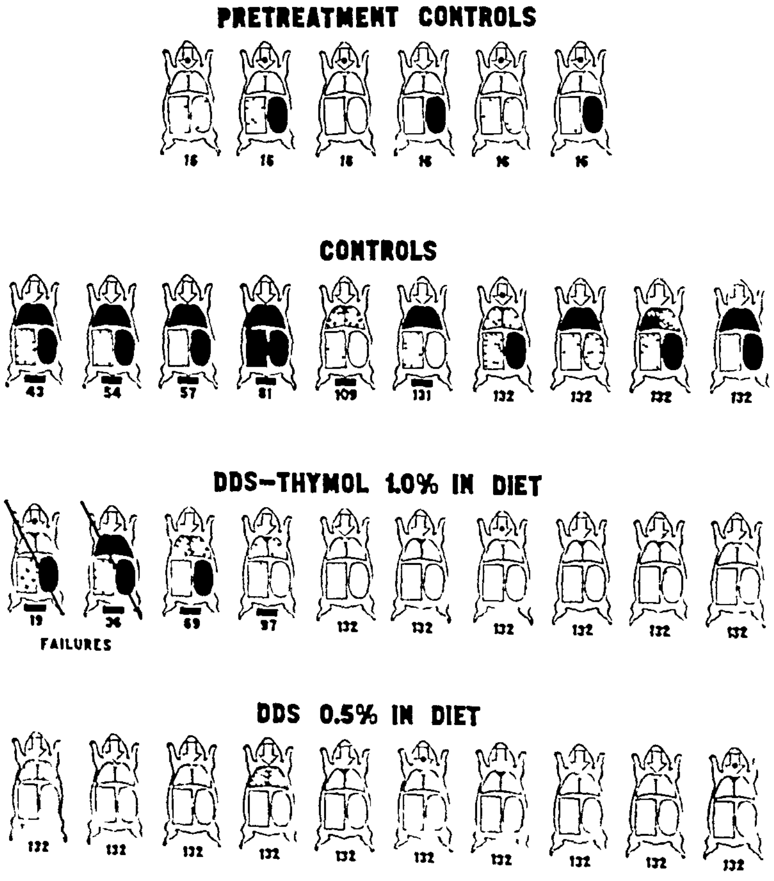


FIGURE 2: Schematic representation of the lesions seen at necropsy. The numbers below each animal indicate the duration of infection in days; the black bar indicates that the animal died. The oval and rectangle represent spleen and liver, respectively; the dots indicate miliary or nodular lesions, whereas complete blackening means diffuse tuberculous involvement. A dot in the arrow indicates involvement of retrosternal lymph nodes. Two animals given DDS-thymol are considered failures because they died prematurely.

In the present study, three animals died after 20, 53 and 81 days of treatment, respectively, with no evidence of any therapeutic effect from DDS-thymol. This may have been the result of poor absorption, which, however, was sufficient for a cumulative effect in animals treated for 116 days. A second possibility is that DDS-thymol does not act directly but owes its effect to liberation of DDS in amounts that are not toxic but are sufficiently great to account for the therapeutic benefit.

SUMMARY AND CONCLUSIONS

Each of 36 guinea pigs was infected intraperitoneally with virulent tubercle bacilli. After 16 days, six were killed and found to have tuberculous lesions. On the same day, the remaining animals were divided into three groups of 10 animals each, namely controls, those treated with 4,4′-diaminodiphenylsulfone (DDS), and those treated with DDS-thymol. Treatment continued for 116 days, at which time all survivors were killed. Six controls had died by this time. All controls, including four survivors, had extensive tuberculosis.

Of those animals treated with DDS-thymol, two died prematurely; two others died after 53 and 81 days of treatment, respectively, and had extensive lesions. Of the surviving six animals, one had a few residual foci in the liver and lungs and two others had microscopically evident lesions in the lungs only. All had caseous lesions in lymph nodes. None of these animals showed any toxic effect from the drug.

None of the animals given DDS died; four had evidence of pulmonary tuberculous lesions. All had caseous foci in the lymph nodes and enlarged cyanotic spleens with dilated sinusoids and many pigment-laden macrophages.

The administration of DDS-thymol to tuberculous guinea pigs resulted in regression of the disease, but the beneficial effect was less than that of DDS. The hematotoxic effects of DDS, as determined by splenic changes, were not seen in animals given DDS-thymol. It was not determined whether DDS-thymol has a direct action or if it is active because of DDS liberated in vivo.

RESUMEN Y CONCLUSIONES

Se infectaron con bacilo tuberculoso virulento 36 cuyes, usando la vía intraperioneal. Después de 16 días, seis se sacrificaron y se encontró que tenían lesiones tuberculosas. El mismo día los animales restantes se dividieron en tres grupos de 10 cada uno o como controles, el segundo grupo se trató con 4,4′-diaminodifenilsulfona (DDS) y el otro grupo con DDS-timol. El tratamiento se prolongó por 116 días a cuyo término se sacrificaron todos los sobrevivientes.

Durante este tiempo murieron seis controles. Todos los controles incluyendo los sobrevivientes tenían tuberculosis extensa.

De los animales tratados con DDS-timol dos murieron prematuramente; otros dos murieron después de 53 y 81 días de tratamiento respectivamente y tenían lesiones extensas. De los sobrevivientes seis animales, uno tenía

un foco residual en el hígado y otros dos tenían lesiones microscópicas evidentes sólo en los pulmones. Todos tenían lesiones caseosas en los ganglios. Ninguno de estos animales mostró efecto tóxico por la droga.

Ninguno de los animales a los que se dió DDS murió; cuatro tenían evidencias de tuberculosis pulmonar. Todos tenían focos caseosos en los ganglios linfáticos y bazos crecidos y cianóticos con sinusoides ensanchados y muchos macrófagos cargados de pigmento.

La administración de DDS-timol a los cuyes tuberculosos produjo regresión de la enfermedad pero el efecto benéfico fué menor que en los tratados por DDS según se determinó por los cambios esplénicos que no se vieron en los que recibieron DDS-timol.

No se determinó si el DDS-timol tiene una acción directa o si es activo por la liberación de DDS en vivo.

RESUME

36 cobayes furent inoculés chacun par voie intrapéritonéale avec des bacilles tuberculeux virulents. Après 16 jours, six furent tués et on constata qu'ils étaient porteurs de lésions tuberculeuses. Le même jour, les animaux restant furent divises en trois lots de dix animaux, les témoins, ceux traités par le 4,4'-diaminodiphénylsulfone (DDS) et ceux traités par le DDS-thymol. Le traitement fut poursuivi pendant 116 jours, au bout desquels tous les survivants furent sacrifiés. Six témoins étaient morts pendant ce temps. Tous les témoins, y compris les quatre survivants, étaient atteints de tuberculose extensive.

Parmi ceux des animaux traités par le DDS-thymol, deux moururent prématurément; deux autres moururent après 53 et 81 jours de traitement avec des lésions extensives. Sur les six animaux survivants, l'un présentait quelques foyers résiduels au foie et aux poumons, et deux autres des lésions visibles microscopiquement uniquement dans les poumons. Tous présentaient des lésions caséeuses dans les ganglions. Aucun de ces animaux ne montra le moindre syndrome toxique imputable à la médication.

Aucun des animaux que avaient reçu du DDS ne mourut; quatre avaient des lésions tuberculeuses pulmonaires évidentes. Tous avaient des foyers caséeux dans les ganglions, et des rates cyanosées et volumineuses, avec des sinus dilatés et chargés de macrophages pigmentés.

L'administration de DDS-thymol aux cobayes tuberculeux a permis la régression de l'affection, mais l'effet favorable fut moindre que celui du DDS. Les effets hémato-toxiques du DDS, comme ils ont été révélés par les altérations de la rate, n'ont pas été constatés chez les animaux traités par le DDS-thymol. Il n'a pas été possible de savoir si le DDS-thymol a une action directe ou s'il est actif grâce au DDS libéré *in vivo*.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Ein jedes von 36 Meerschweinchen wurde intraperitoneal infiziert mit virulenten Tuberkelbazillen. Nach 16 Tagen wurden 6 getötet und bei ihnen tuberkulöse Herde gefunden. Am gleichen Tag wurden die übrigen Tiere in 3 Gruppen von je 10 Tieren eingeteilt, nämlich die Kontrollen,

solche, die mit 4,4'-Diaminodiphenylsulfon (DDS) behandelt wurden, und schliesslich die mit DDS-Thymol behandelt wurden. Die Behandlung wurde 116 Tage lang fortgesetzt und zu diesem Zeitpunkt alle überlebenden Tiere getötet. 6 Kontrolltiere waren während dieser Zeit umgekommen. Alle Kontrolltiere einschl. der 4 Überlebenden hatten eine ausgedehnte Tuberkulose.

Von den mit DDS-Thymol behandelten Tieren starben 2 vorzeitig; 2 andere starben nach 53 und 81 Tagen der Behandlung und hatten ausgedehnte Veränderungen. Von den überlebenden 6 Tieren hatten einige wenige Restherde in der Leber und Lunge, und 2 andere hatten nur mikroskopisch sichtbare Lungenherde. Alle wiesen Käseherde in den Lymphknoten auf. Keines dieser Tiere legte irgendwelche toxischen Wirkungen des Medikamentes an den Tag.

Keines der Tiere, die DDS bekommen hatten, starb. 4 hatten Anzeichen von pulmonalen tuberkulösen Herden. Alle hatten Käseherde in den Lymphknoten und eine vergrösserte cyanotische Milz mit erweiterten Sinus und zahlreichen pigmenthaltigen Makrophagen.

Die Verabreichung von DDS-Thymol an tuberkulöse Merrschweinchen hatte eine Rückbildung der Erkrankung zur Folge, jedoch war die Heilwirkung geringer als diejenige von DDS. Die haematotoxischen Wirkungen von DDS, wie sie sich aus den Milzveränderungen ergaben, war nicht bei den mit DDS-Thymol behandelten Tieren zu sehen. Es wurde nicht ermittelt, ob DDS-Thymol eine direkte Wirkung hat, oder ob es aktiv ist durch in vivo frei gewordenes DDS.

REFERENCES

1 Feldman, W. H., Hinshaw, H. C. and Moses, H. E.: "The Effects on Experimental Tuberculosis of 4,4'-Diaminodiphenylsulfone," *Am. J. M. Sc.*, 207:290, 1944.

2 Doull, J. A.: "Progress in the Therapy of Leprosy," Congresso Internazionale per la Difesa e la Riabilitazione Sociale del "Lebrossa," Rome, April 16-18, 1956, pp. 95-106.

3 Dharmendra: "Chemotherapy of Leprosy," *Indian M. Gaz.*, 88:35, 1953.

4 Francis, J. and Spinks, A.: "Antibacterial Action and Metabolism of Five Sulfones," *Brit. J. Pharmacol.*, 5:565, 1950.

5 Feldman, W. H.: "An Evaluation of the Efficacy in Tuberculosis of Sulfonamides, Sulfones and Certain Other Substances," *J. Roy. Inst. Pub. Health and Hyg.*, 9: 297, 1946.

6 Weiller, Pierre and Rymer, Maurice: "A propos d'une nouvelle sulfone et de son intérêt dans le traitement de la tuberculose pulmonaire," *Poumon, Par.*, 8:747, 1952.

7 Chortis, P.: "La contribution de la sulfone thymolée au traitement de la tuberculose," *Poumon and Coeur*, 11:487, 1955.

8 Salomon, L.: Quoted by Weiller, Pierre and Rymer, Maurice.[6]

9 Rist, Noel, Boyer, Fernand, Saviard, Micheline and Hamon, Viviane: "Sur le mode d'action d'une sulfone thymolée argentique," *Rev. tuberc., Paris*, 18:179, 1954.

10 Urquia, D. A.: "Propriétés bacteriostatiques d'une sulfone thymolée," *Compt. rend. Soc. biol.*, 149:1948, 1955.

11 Feldman, W. H.: "A Scheme for Numerical Recording of Tuberculous Changes in Experimentally Infected Guinea Pigs," *Am. Rev. Tuberc.*, 48:248, 1943.

12 Cotereau, H. Y., Marquiset, J. P., Chaslot, M. and Delamarre, E.: "Recherches biochimiques sur une sulfone thymolée et son dérivé argentique (J51)," *Compt. rend. Soc. biol.*, 149:1142, 1955.

13 Cotereau, H. Y., Marquiset, J. P., Chaslot, M. and Delamarre, E.: "Nouvelles recherches sur la sulfone bisazoique thymolée," *Compt. rend. Soc. biol.*, 149:1950, 1955.

A New Effective Method of Nebulizing Bronchodilator Aerosols: Clinical and Physiological Effects

GUSTAV J. BECK, M.D.,* F.C.C.P.
New York, New York

The use of bronchodilators by nebulization in the treatment of bronchopulmonary disease is recognized to be the most effective and simplest method for control of bronchospasm.

The problem of propulsion of aerosols has been treated in various manner by investigators.[1-3] High pressures needed to achieve the breaking up of solutions into fine particles has been attained in the past by the use of such various devices and propellants as hand bulbs, foot pumps, electric pumps, oxygen and the liquid phase of fluorinated hydrocarbons. The difficulties in coordination between the patient's inhalation and the compression of a hand bulb results at times in failure to achieve a bronchodilator effect of the aerosols administered. The use of the liquid phase of fluorinated hydrocarbon as utilized in a metered valve nebulizer[4] has the disadvantages of difficulty in controlling particle sizes and the irritating effects of the marked cooling of the aerosol produced at the site where the medication is broken up into a stream of fine particles, from where it is carried in its cold state in the pharynx, larynx, and trachea.

The main objective of this study was to establish the usefulness of the gaseous phase of dichlorodifluoromethane** as a means of propelling bronchodilator aerosols. The low degree of toxicity of this gas in mice, rats, guinea pigs, dogs and monkeys[5,6] in concentrations up to 20 per cent in the inspired air with exposure time of seven to eight hours daily for 12 weeks, as well as its nearly ideal physical characteristics, suggests its potential value for this purpose. The good control of aerosol particle size which can be achieved as well as the markedly reduced cooling effect at the site of aerosolization, when the gas phase of dichlorofluoromethane is used, further stimulated interest in the employment of this form of propellant. A clinical appraisal of these theoretical advantages appeared indicated. Determination of the effects of dichlorodifluoromethane on the bronchopulmonary tree, in patients with bronchospasm were thought to be useful. A further object of this study was to utilize a nebulizing unit which would combine the advantages gathered from theoretical considerations of the most effective particle size, with practicability of use for the patient and to determine its effectiveness as compared to other types of nebulizers. A clinical evaluation of a gas phase nebulizer was performed using 0.5 per cent isoproterenol hydrochloride* or 2.25 per cent racemic ephinephrine** as bronchodilators. A series of twenty patients was studied with respect to the inhalation of a mixture of 0.4 per cent isoproterenol sulfate and 2.0 per cent phenylephrine.† These studies were also accompanied by determination of vital capacities, changes in blood pressure and heart rates.

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*From the Department of Medicine, Columbia University, College of Physicians and Surgeons and the Presbyterian Hospital of New York.

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**The gas phase of dichlorodifluoromethane is 99.98 per cent pure, and contains no hydrocarbons; cartridges containing this gas were supplied as Halon® (formerly Halothane) by Thomas J. Mahon, Inc., Englewood Cliffs, New Jersey.

Introduction and Methods

Since the introduction of aerosols for the treatment of bronchospasm several definite principles have been established. Two of the principles concerned the deposition of particles in the tracheobronchial tree:[1, 7]

1. The smaller the particle size of aerosol above 0.8 micron, the closer to the alveoli and to the alveolar ducts its deposition in the lungs; the larger its size the higher its rate of deposition in the upper respiratory tree.
2. The smaller the particle size, the lower the per cent of retention in the lung, a condition which prevails when the diameter of the particle is between 0.2 and 0.6 microns.[8, 9]

It has been recommended[10] that 50 per cent or more of the particles delivered have a range of diameter between 1 and 5 microns. The experimental attempts to achieve this particle size, utilizing the liquid phase of fluorinated hydrocarbon as a propellant have been unsuccessful. A high percentage of larger particles causes the aerosol to be "wet," thereby producing deposition of a large proportion of the drug-fluorinated hydrocarbon mixture in the upper respiratory tract, causing throat irritation. The observation that the gas phase of dichlorodifluoromethane, exerting an absolute pressure of 70 lbs. per square inch at 21°C., offered an excellent and well tolerated source of propulsion led to the development of a simple experimental nebulizer (Fig. 1A). Two pocket sized cartridges containing 51 and 100 gms. of *dichlorodifluoromethane*, respectively, in its liquid-gas equilibrium were utilized as sources of propulsion. Since the pressure exerted by dichlorodifluoromethane gas does not vary with the amount of liquid or gas present in a cartridge, 70 lbs. per square inch is available for propulsion of the aerosol, as long as any amount of dichlorodifluoromethane is present within the cartridge. Through a lateral displacement valve the pressure available from the cartridge is transmitted to a nebulizer, which by venturi action picks up the bronchodilator from a small well and throws it against a baffle, thereby breaking it up into a desirable size of particle. Activation of the valve was simply effected by slight sideways pressure of the nebulizer. An air vent in the back of the venturi-baffle device of the nebulizer served, in the manner of a carburetor, to increase the impact of the bronchodilator stream against the baffle, thereby still further decreasing particle size, and also increasing the total aerosol flow into the patient's mouth by admixture of air to the propellent gas. A further modification of this type nebulizer was developed in which a replaceable cartridge and nebulizing unit are contained within one small plastic unit, in which the release of dichlorodifluoromethane is effected by slight displacement of the cartridge, rather than the nebulizer, using slight pressure of the thumb.* In addition, this unit has the advantage of replaceable capillaries, easy access to the interior of both the cartridge chamber and the aerosol well for cleaning purposes (Fig. 1B).

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*0.5 per cent isoproterenol hydrochloride (Nepu-Prel) and a mixture of 0.4 per cent isoproterenol sulfate and 2.0 per cent phenylephrine in 10 per cent propylene glycol (Nebu-prel with phenylephrine), were supplied by Thomas J. Mahon, Inc., Englewood Cliffs, N. J.

**2.25 per cent racemic epinephrine (Vaponefrin) was supplied by Vaponefrin Co., Upper Darby, Pennsylvania.

†cf. Foot Note ** on page 2.

The patient is instructed to activate this unit by slight pressure of the thumb against the cartridge through the hole in the cartridge housing,

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*Nebu-Halent® "Touch-Action" Nebulizer, as supplied by Thomas J. Mahon, Inc., Englewood Cliffs, N.J.

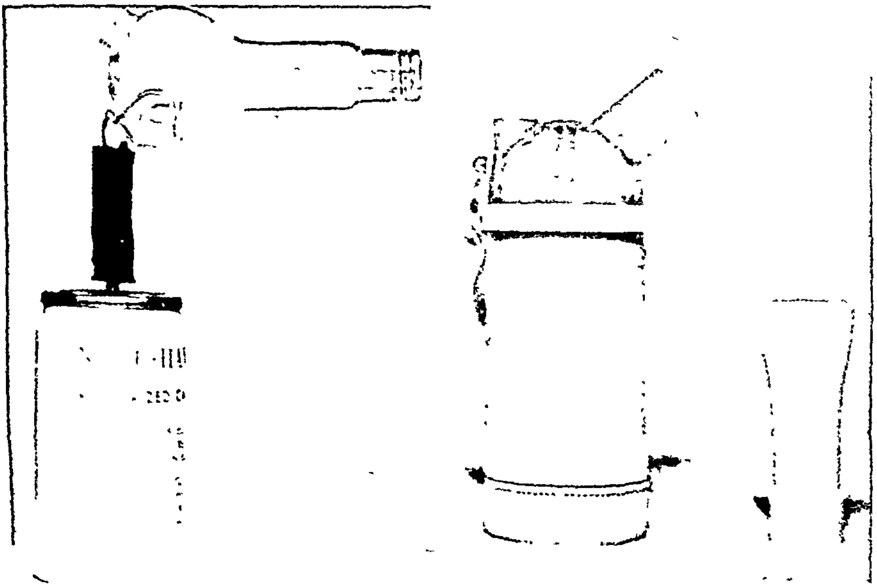

FIGURE 1A FIGURE 1B

Figure 1A: Halon® gas phase propelled nebulizer. Experimental model.—*Figure 1B:* Halon® gas phase propelled nebulizer. Clinical apparatus.

simultaneously with the initiation of his own inspiration, placing the spout of the nebulizer about one inch in front of the mouth.

Dichlorodifluoromethane concentrations inhaled during the process of aerosolization were measured in the following manner: A plastic catheter was introduced through the nose into the subject's pharynx, about 1 cm. above the epiglottis. The gas sample was collected in a mercury sampling bottle slowly throughout each of five consecutive inspirations, while the subject was inhaling the gas mixture from the nebulizer. The sampling bottle then was emptied through the catheter to wash out the dead space with inspired air. The procedure was then repeated. The gas sample thus collected was analyzed for oxygen and carbon dioxide, using the Scholander Method of Analysis.* The concentration of dichlorodifluoromethane in the inspired air calculated from the reduction in the oxygen concentration in the sample from that of ambient air, was 3.7 per cent. Up to 8.1 per cent of dichlorodifluoromethane were obtained during the early part of the inspiration when the gas samples were collected under vacuum.

The studies determining the particle size produced by the unit were conducted using a cascade impactor** 0.5 per cent isoproterenol hydrochloride solution to which radioactive and phosphorus-32 was added in the proportions of 250 microcuries P 32 to 10 cc. of bronchodilator.

Vital capacity studies were performed graphically in some patients, by using a 9 liter spirometer and by means of inflation of a McKesson Scott Ventilometer in others. The vital capacity, heart rate and blood pressure measurements were carried out immediately before, and 10 to 15 minutes after the inhalation of the aerosol. The patients were selected strictly at random† in all experiments to determine which medication they should receive.

Isoproterenol hydrochloride and 2.25 per cent racemic epinephrine were selected as bronchodilators in this study because of the known high degree of effectiveness of these medications in resolving bronchospasm.[1, 3, 11-13] A quantitative comparison of the effectiveness of these bronchodilators when inhaled by the dichlorodifluoromethane gas phase propelled nebulizer was attempted. Additional information concerning differences in the physiological effects of these two drugs in pulmonary emphysema and bronchial asthma, with particular reference to vital capacity, blood pressure, heart rates, and the side effects, was thought to be desirable. A mixture of 0.4 per cent isoproterenol sulfate and 2 per cent phenylephrine hydrochloride, administered in the same manner was similarly studied to determine the possible advantages of the addition of a vasoconstrictor to a bronchodilator aerosol.[1]

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*The gas analyses were performed in the Laboratories of Doctor Duncan Holaday, Department of Anesthesiology, Columbia University, College of Physicians and Surgeons, New York, N.Y.

**This study was performed at the Battelle Memorial Institute, Columbus, Ohio, by R. I. Mitchell.

†The term "strictly at random" has been recommended by D. Mainland, *Chance and Random Sampling, Methods in Medical Research*, Vol. 6, 1954, J. Murray Steele, Ed., The Year Book Publishers. It signifies the selection of samples by means of an unbiased method of chance, e.g., the throw of a coin.

Results

Ten patients with bronchial asthma and pulmonary emphysema were given five inhalations of dichlorodifluoromethane from the nebulizing unit described, without the addition of a bronchodilator. The chest was examined and vital capacities performed before and 10 minutes after the inhalation of the propellant. The patients were also asked if they noted any side effects. The results summarized in Table I, revealed that dichlorodifluoromethane produced no significant changes in vital capacity. Only one complained about the odor of gas, stating that it resembled that of ether and that he never liked ether. The degree of wheezing remained the same in all, except in two where it seemed that a slight diminution had taken place, and that there was slightly diminished dyspnea.

One hundred patients with bronchial asthma or pulmonary emphysema were supplied with dichlorodifluoromethane propelled units and either 2.25 per cent racemic epinephrine or 0.5 per cent isoproterenol hydrochloride for use at home over periods of one to six months. The following information was requested from the users:

1. Number of daily single inhalations.
2. Number of total inhalations which could be obtained from one single Halon® cartridge.
3. Comparison of effectiveness and ease of administration of the dichlorodifluoromethane propelled with other types used before.

The average number of daily single inhalations using dichlorodifluoromethane cartridges was 24. The average number of days of use of one cartridge was nine. No respiratory tract or gastrointestinal tract irritation was observed. The etheral odor of dichlorodifluoromethane was found objectionable by three patients. Headache was reported in two patients, dizziness by the same two patients and one additional patient. The latter also described faintness and tremors following the use of bronchodilator aerosols in general. For this reason he was tested in the clinic using five inhalations of dichlorodifluoromethane without the bronchodilators; he had none of these side reactions under these circumstances. Similarly, six others who reported tremulousness and palpitation following five inhalations of bronchodilator aerosols reported none of these symptoms if dichlorodifluoromethane was inhaled without a bronchodilator or if the number of inhalations with bronchodilators was reduced to two or three per treatment. They all had, also, a good bronchodilator response from this diminished dose.

Thirty-two patients, described better bronchodilating effects from the gas phase type nebulizing unit than with any other type unit used up to that time. Better coordination between their own inspiration and activation of the dichlorodifluoromethane propelled nebulizer probably accounted for this observation. Two refused to continue using the equipment, both because of headache, faintness and dizziness following its use.

Determination of the particle size and distribution of the number of particles in various ranges are summarized to Table II.* The mass median diameter of the particles produced by the dichlorodifluoromethane gas phase propelled nebulizer with the air vent open was 1.9 microns. The weight fractions of particles having a diameter of 1 to 5 microns was 70 per cent, that fraction containing large particles of a diameter of 5 microns being only 14 per cent.

Determinations of the amounts of 0.05 per cent isoproterenol hydrochloride solution aerosolized revealed that 0.012 mg. were inhaled per breath.

Vital capacity determinations performed before and 10 minutes after five single inhalations of isoproterenol hydrochloride and 2.25 per cent racemic epinephrine in patients with pulmonary emphysema and bronchial asthma, are summarized in Table III and IV. The mean per cent increase over the control value were 36 per cent in bronchial asthma and 34 per cent in pulmonary emphysema for 2.25 per cent racemic epinephrine, and 30 per cent in bronchial asthma and 29 per cent in pulmonary emphysema for 0.05 per cent isoproterenol hydrochloride. The difference as calculated by determining t-values were statistically insignificant for the two bronchodilators in bronchial asthma or pulmonary emphysema.

The blood pressures of patients using isoproterenol hydrochloride and racemic epinephrine by this method of aerosol administration were studied in normotensive and hypertensive patients with bronchial asthma before and 15 minutes after administration and over a period of three months. The results are summarized in Table V. The mean systolic and diastolic blood pressure differences, before and 15 minutes after administration of five inhalations of these two bronchodilator drugs, normotensive and hypertensive patients were not significant. In twenty patients in whom three inhalations of the 0.4 per cent isoproterenol sulfate and 2.0 per cent phenylephrine was given a single treatment in the office or the Out-Patient Department the clinical results were good. This patient group included those with pulmonary emphysema and bronchial asthma, many of whom were getting worse on routine therapy. An increase in vital capacity occurred in all instances (Table V). In an additional group of ten patients, in which five inhalations of this compound was administered, a somewhat more pronounced improvement took place both to subjective relief and vital capacity change. In patients to whom isoproterenol combined with phenylephrine was administered sinus tachycardia was not observed. No significant change in blood pressure was found (Table VI).

Sinus tachycardia occurred in five patients (10 per cent) following five inhalations of isoproterenol hydrocloride, and in three patients (6 per cent) using 2.25 per cent racemic epinephrine. The incidence of tachycardia was not related to the presence of either hypertension or heart disease. In no instance did the heart rate exceed 130 beats per minute. Palpitation occurred in one of these patients using isoproterenol hydrochloride.

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*This study was performed at the Battelle Memorial Institute, Columbus, Ohio, by R. I. Mitchell.

Discussion

The frequent use of dichlorodifluoromethane as a refrigerant and the reported low degree of toxicity in animals by inhalation in concentrations up to 20 per cent warranted its use as a propellant for bronchodilator aerosols. It would appear from this study that the compound in concentrations of about 4 per cent in the inspired air behaves as an inert gas as far as its inhalations by patients with bronchial asthma and pulmonary emphysema are concerned.

A device was designed utilizing the gaseous phase of dichlorodifluoromethane as a propellant and incorporating the advantages of nebulizers known to exist, including dispersion into desirable particle size, efficiency of pick-up of aerosol by the capillary of the venturi, simplicity in activating the nebulizer and exchangeability of capillaries.

The observations of the effectiveness of aerosols administered by this method as measured clinically and by means of vital capacity measurement may be ascribed to greater ease of coordination between activation of the device and the patient's initiation of inspiration. High volume flow rates occurring during the first part of inspiration in patients with bronchospasm carry the aerosol particles of optimal particle size to the small bronchi.

The absence of short or long term effects on the blood pressure of normotensive and hypertensive patients of inhaled isoproterenol hydrochloride with and without phenylephrine and 2.25 per cent racemic epinephrine is of clinical importance. One may conclude from the findings in this series that the use of these sympathomimetic amines in hypertensives has little or no deleterious effect on the level of either the systolic or the diastolic blood pressure, if the range of the particle size is sufficiently controlled to permit deposition of a majority of particles on the bronchial mucosa. It is noteworthy that the bronchodilator compound containing both isoproterenol sulfate and phenylephrine did not appear to produce the tachycardia observed at times after the employment of the preparations noted above. Additional studies of this bronchodilator aerosol are in progress.

SUMMARY

The gas phase of dichlorodifluoromethane is a well tolerated and expedient propellant for use in the nebulization of bronchodilator aerosols. Inhalation in concentrations of approximately 4 per cent in patients with bronchospasm produces no change in vital capacity. Side reactions from

the inhalation of these low concentrations of dichlorodifluoromethane are minimal and occur infrequently.

Studies of the effect of 0.5 per cent isoproterenol hydrochloride and 2.25 per cent racemic ephinephrine when inhaled in the form of an aerosol by means of a gas phase of dichlorodifluoromethane propelled nebulizer revealed clinical relief of dyspnea and corresponding increases in vital capacity. The number of side reactions to these bronchodilators was low and confined to tremulousness and tachycardia. Reduction in the amount of drug inhaled reduced the incidence of side reactions. The use of the bronchodilator solution in which 0.4 per cent isoproterenol sulfate was combined with 2.0 per cent phenylephrine was not followed in this series with either tremulousness or tachycardia. Neither drug caused change in the blood pressure of normotensive or hypertensive patients when nebulized with this type device.

RESUMEN

El diclorodifluorometano en fase gaseosa, es un propulsor bien tolerado y rápido para uso en nebulizacion de aerosoles broncodilatadores. Su inhalación en concentraciones de aproximadamente un 4 por cineto en pacientes con broncoespasmo, no produce ningún cambio en la capacidad vital.

Efectos secundarios a la inhalación de estas bajas concentraciones de diclorofluorometano son minimas y ocurren raremente.

Estudios del efecto de 0.5 por ciento de hidrocloruro de isoproterenol y 2,25 por ciento de epinefrina racémica inhalados en forma de aerosol por medio de una fase gaseosa de diclorodifluorometano como propulsor nebulizador, reveló alivio clinico de disnea y subsecuente aumento de la capacided vital. El numero de efectos secundarios a estos broncodilatadores fué bajo y confinado solamente a temblor y taquicardia. Reducción de la cantidad de droga inhalada redujo la incidencia de efectos secundarios. El uso de una solución bronco-dilatadora en la cual 0,4 por ciento de sulfato de isoproterenol fué combinado con 2,0 por ciento de fenilefrina no fué seguido en estas series de temblor ni de taquicardia.

Ninguna de las dos drogas causo cambio en la presión sanguinea en pacientes normo o hipertensos caundo fueron nebulizades por este procedimiente.

RESUME

La phase gazeuse de dichlorodifluoromethane est bien tolerée et commode pour ultilization come propellant pour les aerosols bronchodilateurs. L'inhalation de cette gaz, en concentration d'environs quatre pour cent pare des malades avec du spasm des bronches ne produit pas de change en capacité vitale. Les effets secondaires de cette gaz aux concentrations basses sont minimals et recontrés rarement.

Les études des effets de l'inhalation de 0.5 pour cent de l'hydrochloride de isoproterenol et de 2.25 pour cent d'epinephrine racemic pare moyen

d'aérosolization avec un appareil aérosolisateur activé par la phase gazeuse de dichloro-difluoromethane ont demonstrées l'amélioration de la dyspnée et des augmentations attendantes de la capacité vitale. Les èffets secondaires de ces bronchodilateurs sont minimales et consistent des tremeurs et de tachycardie. La reduction des quantités des bronchodilateurs inhalés cause l'élimination de ces effets secondaires. L'utilisation d'une solution de 0.4 pour cent de sulfate d'isoproterenol en combination avec 2 pour cent de phenylephrine ne produisaient aucune réaction secondaire. Aucune de ces bronchodilateurs produisaient des changes dans la pression arterielle ds sujets normals ou hypertensive, lorsqu'ils étaient aerosolisés avec cet appareil d'aérosolisation.

ZUSAMMENFASSUNG

Dichlordifluoromethan in seiner Gas Form is ein gut tolerierter und leicht erhaltbarer Propellant für die Verstäubung der bronchodilatierenden Aerosols. Die Einatmung von 4% Dichlodifluoromethan in Patienten mit Asthma haben keinen Einfluss auf die Vital Kapazität. Nebenwirkungen mit Anwendung dieser niedrigen Mischungen waren minimal un wurden nur selten beobachtet.

Wenn 0.5% Isoproterenol oder 2.25% razamisches Epinephrin als Aerosol inhaliert wurden mit einem Gas-Phase Dischlorodifluoromethan betriebenem Versotäubungs Apparet wurden ausgezeichnete Erleichterung der Kurzatmigkeit und Erhöhung der Vital Kapazitat beobachtet. Nebenwirkungen wurden selten befunden und bestanden aus Zittern und Herz Beschleunigung. Wenn etwas weniger von diesen Medikamenten inhaliert wurden verschwunden diese Nebenwirkungen. Eine Mischung von 0.4% Isoproterenol sulfat und 2.0% Phenylephrin, wenn inhaliert, was niemals von diesen Nebenwirkungen begleitet. Keines diese drei verschiedenen Medikamenten erhöht den Blutdruck normaler oder hypertensiver Patienten, wenn inhaliert mit diesem Apparat.

REFERENCES

1 Barach, A. L.: "Physiologic Therapy in Respiratory Disease," *J. B. Lippincott Co.*, Philadelphia, 1948.

2 Miller, W. F.: "A Consideration of Improved Methods of Nebulization Therapy," *Jour. Am. Med. Assn.*, 251:581, 1954.

3 Levine, E. R.: "Aerosol Therapy in the Management of Bronchopulmonary Infection Including Exsufflation;" in *Pulmonary Emphysema*; Editors: Barach, A. L and Bickerman, H. A., *Wilkins & Williams Co.*, Baltimore, 1956.

4 Unger, L. and Unger, A. M.: *J.A.M.A.*, 150:562, 1952.

5 Sayers, R. R., Yant, W. P., Chornyak, J. and Shoaf, H. W.: "Toxicity of Dichloro-Difluoromethane: A New Refrigerant," *Report of Investigation of Dept. of Commerce*, U.S. Bureau of Mines, R.I., 3013, May 1930.

6 Greenberg, L. and Lester, A.: "Acute and Chronic Toxicity of Some Halogenated Derivatives of Methane and Ethane." *Arch. Ind. Hyg. and Occ. Med.*, 2:335, 1950.

7 Dautrebande, L., Catry, D., Van Verkam, J. and Cereghetti, A.: "Essai de prevention Dela Silicase," *Union Miniere du Houst Katanga*, 1954 (Ref. 17).

8 Talbot, T. R., Jr., Quimby, E. H. and Barach, A. L.: "A Method of Determining the Site of Retention of Aerosols Within the Respiratory Tract of Man by the Use of Radioactive Sodium," *A.J.M.Sc.*, Dec. 1947.

9 Barach, A. L., Garthwaite, B. and Bickerman, H. A.: "Postgraduate Medicine," 5:314, 1949.

10 Abramson, H. A.: "Principles and Practice of Aerosol Therapy of the Lungs and Bronchi," *Ann. Allergy*, 4:440, 1946.

11 McKee, K. T. and Mosley: "The Use of Isuprel in the Treatment of Asthma," *J. So. Carolina Med. Assn.*, 46:72, 1950.

12 Cohen, E. N. and Van Bergen, F.: "Isuprel, A New Bronchodilating Agent," *Bull. Univ. Minn. Hosp.*, 19:424, 1948.

13 Gay, L. N. and Long, J. W.: "Council on Pharmacy and Chemistry," *Jour. A.M.A.*, 139:452, 1949.

Tables I-VI will appear in reprints.

General Anesthesia in Bronchoesophagology, A Review of Its Use in 4,000 Endoscopic Procedures Over a Ten Year Period

C. B. SCHOEMPERLEN, M.D., F.C.C.P.
Winnipeg, Manitoba, Canada

It is well recognized that local anesthesia is used by most endoscopists on this continent and in England. It is the method of choice recommended in all text books dealing with bronchoesophagology and diseases of the chest;[1-6] Jackson and Jackson,[1] in 1934 stated, "General anesthesia is never used in our Clinic for endoscopic procedures." In recent years, however, with continuing improvements in methods and drugs used in general anesthesia, this method has gained some increase in favor, particularly in esophagoscopy and is even recommended for beginners in esophagology, by Jackson,[2] in 1950. Holinger[7 8] also suggests its use in certain instances.

Although local anesthesia has proved to be extremely valuable in endoscopy it has limitations and dangers. Some of these have been referred to by Thomas and Fenton,[9] Weisel and Tella,[10] and Lierle.[11]

While serving overseas in a 600 bed hospital, the author did bronchoscopies and esophagoscopies under local anesthesia, as previously taught and practiced. However, our anesthetist, the late Dr. A. St. C. Rumball,[12] was responsible for my initial interest in general anesthesia for endoscopic procedures. We used pentothal anesthesia (sodium thiopentone) many times, but as many others have found,[13] we also observed that pentothal alone or in conjunction with local anesthesia was not satisfactory. We encountered many cases of laryngospasm and the patients had to be in a dangerously deep stage of anesthesia before they were sufficiently relaxed, particularly for bronchoscopies. We found that ether even without preliminary local gave excellent relaxation, but as these patients were all active, young, and usually healthy men, ether anesthesia was too time consuming in a busy military hospital. We eventually abandoned the idea, but happily fate brought us together again in Winnipeg, following hostilities, when we were both appointed to the staff of Deer Lodge Veterans' Hospital at the beginning of January, 1946. We eventually developed a method mutually satisfactory to both of us. The paper published by Cassels and Holinger,[7] in 1946 on "Points of Mutual Interest in Bronchology and Anesthesiology" brings back many fond memories and adequately describes our associations of that time. Our experience at Deer Lodge was confined to adults but at the same time the author was appointed to the staff of the Winnipeg General Hospital, and a little later to the Children's Hospital of Winnipeg, so that ample opportunity was provided to use

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From the Department of Medicine, University of Manitoba, and the Department of Medicine and Endoscopy, Deer Lodge Veterans' Hospital, Winnipeg General Hospital, Children's Hospital of Winnipeg and Manitoba Clinic.

general anesthesia for endoscopic procedures at all three hospitals, and I am very grateful to the anesthetists in all of these hospitals, who have been most cooperative and helpful, with useful suggestions and criticisms. More articles appeared in the literature,[14-23] describing the use of pentothal and curare, or allied relaxants. These were studied with interest and many of them appear in the bibliography.

Clinical Material

This review covers a period of approximately 10 years, from January 1946 to the end of September 1956 with personal records of 5,578 bronchoesophagological procedures, and of these 4,212 were carried out under general anesthesia. The remainder were done under local or without anesthesia, but are not considered in this review.

The choice of anesthetic depends on many factors, particularly the availability of an anesthetist and one that is willing and anxious to give anesthesia for endoscopy. It is also advantageous to have adequate recovery room space, and personnel to watch these patients until they have reacted sufficiently from the anesthetic. This has necessitated some changes in our plans and methods from time to time, since as is well known there is becoming a greater shortage of hospital space and it is not possible sometimes to observe the patients in a recovery room close to the operating room. When this condition arises we often use local anesthesia alone or with nisentil, to expedite the procedures and accommodate the hospital staff. It is not the intention to suggest that people who are familiar and satisfied with local anesthesia should change to general anesthesia. It is merely the purpose to present these cases that have been done under general anesthesia to illustrate that the method is as safe as local anesthesia alone.

The necessity of having an anesthetist who is interested and anxious to give anesthesia for endoscopy must be emphasized.

TABLE I
TOTAL PROCEDURES DURING A TEN-YEAR PERIOD (1946-1956)
CLASSIFIED AS TO YEAR, SEX AND TYPE

Year	Number of Procedures	Male	Female	Bronchoscopy	Esophagoscopy
1946	140	126	14	129	11
1947	343	295	48	300	43
1948	383	332	51	303	80
1949	425	336	89	313	112
1950	355	286	69	272	83
1951	442	319	123	317	125
1952	488	326	162	377	111
1953	493	343	150	382	111
1954	508	320	188	405	103
1955	364	206	158	293	71
1956	274	163	108	230	41
TOTAL	4,212	3,025	1,160	3,321	891

Table I illustrates the incidence according to year, sex and type of procedure. The ratio of three men to one woman is only partially explained by the fact that in a veterans' hospital most of the patients are men. Those done in the Veterans' Hospital constituted only about one-third of the total procedures. About one-quarter were esophagoscopies, the remainder bronchoscopies. In some cases both procedures were done, although these are not shown in the Table. In these cases the esophagoscopy is done first. Also, some patients have been done repeatedly. One girl who was 18 months old at the first bronchoscopy was done 25 times for the purpose of tracheal dilatation. One man had been bronchoscoped 31 times under local, pentothal and curare.

Table II divides the cases into three age groups. This was done to show that a fair number of children were given general anesthetics. All of these children under 10 (450), were given ether alone, or in combination, except one child of eight who was bronchoscoped under pentothal and flaxedil. The Table also illustrates that there were a considerable number of elderly people (386) over 70 years. The eldest receiving pentothal was 89 years. The largest group was from 10 to 69 years of age (3,376), and it was in this series that pentothal and curare gained prominence and proved to be most useful.

Preoperative Medication

Almost all patients were admitted to hospital the evening before operation, except emergency cases, particularly foreign bodies, which were done immediately. Adults were usually given barbiturate sedation the night before. Breakfast was withheld in the morning and all adults were given a hypodermic one hour preoperatively. At the Winnipeg General Hospital, morphine gr. ⅛, gr. ⅙ or gr. ¼ was given according to the usual methods of assessment. This is usually given along with atropine gr. 1/150. However if the individual is asthmatic or has many secretions that we wish to aspirate we do not give atropine. We also omit morphine

TABLE II
AGE DISTRIBUTION FOR THE TOTAL SERIES (4,212)

Year	Under 10 Years	10 - 69 Years	70 Years and Over
1946	4	129	7
1947	3	323	17
1948	38	322	23
1949	52	338	35
1950	36	281	38
1951	35	348	59
1952	52	384	52
1953	56	393	44
1954	65	396	47
1955	56	268	40
1956	53	194	24
TOTAL	450	3,376	386

in asthmatics. At Deer Lodge Veteran's Hospital a combination of pantopon, gr. 1/3 and scopolomine gr. 1/150 is used one hour preoperatively. This dosage may be adjusted up or down as necessary. Infants are given no preoperative hypodermic. Children under 10 are sometimes given atropine preoperatively and occasionally a small dose of one of the barbiturates. Adrenalin by hypodermic, intravenous or rectal aminophyllin or hydrocortisone may be given to asthmatics preoperatively when indicated.

For a short period a barbiturate was given to adults two hours preoperatively but this was soon discontinued as it was felt that not only was it not necessary, but occasionally it made the patient too drowsy and it was felt that we had to keep some of these patients too long in the recovery room following pentothal in addition to the previously given oral barbiturate. Intravenous pentothal is an excellent antidote to any adverse reaction one may encounter from the topical agent.

Postoperatively we leave routine orders for nothing orally for two hours. However, usually by the time the patient has reacted from the general anesthetic it is safe for him to take water if he so desires.

Preliminary Topical Anesthesia

Almost all of our patients receiving pentothal first have topical anesthesia in the form of a spray and direct application by pledget into the pyriform fossae. These pledgets are wet enough to allow excess local to run into the larynx and therefore into the trachea. Occasionally if the mucosa appears sensitive we instil one cc. by cannula into the larynx. At Deer Lodge Hospital the anesthetic staff is partial to transtracheal local, and in this hospital after the patient has had the spray and applicators the anesthetist instils 1 or 2 cc.'s of the local by needle transtracheally. I personally feel that this is not necessary when one is using a

TABLE III
ANESTHETIC AGENTS EMPLOYED

Year	Pentothal	Local and Pentothal	Pentothal and Curare	Local Pentothal and Curare*	Ether**
1946	5	16	76	38	5
1947	1	1	206	130	3
1948	1	6	90	248	38
1949	0	2	2	362	56
1950	1	2	1	296	54
1951	0	4	1	384	48
1952	2	0	2	446	60
1953	1	3	4	416	70
1954	3	17	0	390	98
1955	8	22	3	235	99
1956	12	45	0	142	85
TOTAL	34	118	385	3,087	616

*This includes Curare and Curare-like drugs. See Table IV.
**This includes Ether alone and in combination. See Table V.

general anesthetic. However we have had no ill effects from it, and I therefore do not object.

Type of Local Anesthesia.—To the end of January 1952, 2 per cent pontocaine (tetracaine) was used in the spray, and ½ per cent pontocaine on the local applicators and for the intratracheal instillations. Cyclaine (hexyclaine) 5 per cent then became available and since February 6, 1952 we have used it almost exclusively. It appears to act more rapidly, is more effective. According to Orkin and Rovenstine,[24] it is safer than pontocaine.

Anesthetic Agents and Methods

Table III shows the trend by year of the different methods used. Pentothal was used only when the patient was old, debilitated, or extremely ill, where he objected to having a local spray or was known to have a sensitivity to local but where it was deemed advisable to have him asleep.

The second column in Table III shows that 118 cases were given local and pentothal only. Of these, sixteen were in 1946, when we were first starting to use curare and the number of cases again increased in 1954, 1955 and 1956. The reason for this is that we have found in some of our older patients, where we formerly used pentothal alone, we are now using local and just enough pentothal to have the patient asleep, and getting along well. Curare is not necessary in many of these elderly patients if preliminary local is used.

The third column in Table III shows our early attempts to use pentothal and curare without preliminary topical. This method was given a fair trial (206 times in 1947), but as stated previously larger quantities of pentothal and curare were required to achieve adequate relaxation, and consequently the reaction period following anesthesia was prolonged, and this method was therefore abandoned for the local, pentothal, curare combination.

Local Pentothal and Curare-like Drugs.—Table IV is a more detailed breakdown of the various types of muscle relaxants used in combination with local and pentothal. Curare is marketed by E. R. Squibb and Company under the name of Intocostrin, which is a purified extract of crude curare (purified chondodendrom tomentosum extract). and is packaged 20 units to the cc. We used this originally, and then later used d-Tubocurarine chloride, 3 mgm. to the cc. which is equivalent to 20 units of intocostrin. This is a pure substance and assayed by weight. In February 1952 we started to use flaxedil, tri (B-diethylaminoethoxyl) 1, 2, 3, benzene triodoethylate. This is synthetic curare marketed by Poulenc, Limited, 20 mgm. per cc. When succinylcholine chloride was marketed we first used it in 1952 under the trade name of anectine chloride, Burroughs Wellcome & Company, 20 mgm. to the cc. Succinylcholine is also marketed by Abbott under the trade name of Quelicin, and by Baxter under the name of rubilexin. When the anectine drip is referred to, a solution was made of 500 mgm. of succinylcholine in 500 cc.'s of 5 per cent glucose and saline.

Preferably we first apply the local as previously described. The 2½ per cent pentothal is then started intravenously and when the patient becomes unconscious the relaxant is injected separately into the tubing or the vein. We prefer curare or flaxedil; 1 or 2 cc.'s is given. We then wait two or three minutes and if further relaxation is required the relaxant is given in no greater quantity than 1 cc. at a time. If more pentothal is required, it too is given slowly. It is important that the pentothal and relaxant be kept in different syringes. Once the jaw is properly relaxed and the bronchoscope or esophagoscope is introduced we rarely require any more relaxant, just enough pentothal is used to keep the patient asleep or anesthetized only sufficiently for the endoscopist to continue his operation. Oxygen may be given continuously through the sidearm of the bronchoscope, and the concentration may be increased by closing the end of the bronchoscope with the thumb. We try to inform the anesthetist when we expect to be finished so that he will have the patient almost awake by the time the instrument is withdrawn.

Anectine 20 mgm. to the cc. in a syringe, and by the drip method was given a trial but we found that the margin of safety between proper relaxation and complete apnoea was too small. The actual dose by drip method was difficult to assess or control. On occasions we would have to withdraw the bronchoscope and either have to intubate or use oxygen by mask and bag to control respirations. In other words, although it is safe where the patient is previously intubated so that controlled respiration can be carried out, this is not practical where one requires to use the airway for the bronchoscope. Its use in esophagology was discontinued because it is rarely necessary to intubate a patient during esophagoscopy under pentothal or ether anesthesia. A large Roberts type esophagoscope is used and it is much easier to introduce if the patient does not have an endotracheal tube. Only occasionally, where pressure on the larynx may interfere with respiration, is intubation done and this is usually only necessary when one is working at the distal end of the esophagus.

TABLE IV

TYPE OF MUSCLE RELAXANT USED IN COMBINATION WITH LOCAL AND PENTOTHAL IN 3,087 CASES

Year	Curare	Flaxedil	Anectine	Anectine Drip
1946	38			
1947	130			
1948	248			
1949	362			
1950	296			
1951	384			
1952	424	17	5	
1953	129	279	9	8
1954	50	305	12	23
1955	5	215	8	7
1956	0	140	1	1
TOTAL	2,057	956	35	39

Presently then we are using cyclaine 5 per cent topically, pentothal and flaxedil intravenously. It must be emphasized that these reagents are potent and must be used with great care. We have very occasionally encountered laryngospasm or bronchospasm postoperatively, but these are usually overcome with an oxygen mask or by lying the patient on his side or allowing him to sit up. If one waits for proper depth of anesthesia and relaxation before attempting to instrument the patient, laryngospasm will rarely if ever occur pre- or postoperatively. It has rarely been necessary to use curare antagonists,[25] prostigmine or tensilon chloride (edrophonium chloride) marketed by Hoffmann-La Roche, Inc. Asthma is a contraindication to the use of pentothal and curare and curare should be used sparingly, if at all in elderly and debilitated patients. It might also be reiterated that one must be on the lookout for myasthenia gravis where curare is of course contraindicated. Again we arbitrarily use 10 years of age as a minimum for the use of combined local pentothal and curare. Pentothal is not inflammable or explosive. It is an excellent antidote for any reactions one may get from the topical and in fact must reduce the incidence of such reactions.

To summarize then, curare or one of the curare like drugs was used in combination with local and pentothal in 3,087 procedures, and used in combination with pentothal but without local in 385 procedures. In this series there was one death, in June 1949. This was a 25 year old man who had been in the hospital almost continuously for three years with severe asthma. When first seen the morning of his death he had been in status asthmaticus and severe respiratory acidosis for two weeks. It appeared he had irreversible pulmonary damage and bronchoscopy was not done. Early that evening however at the insistence of his attending physician he was to have been bronchoscoped under ether which might have relieved his persistent bronchospasm. Unfortunately the anesthetist was not prepared to give ether and instead gave him 1.7 cc. of curare and 0.17 gm. of pentothal. Cardiac and respiratory arrest followed immediately and he could not be revived. Micropsy revealed over distended lungs and most of the small bronchioles were occluded with bronchiolar casts. Subsequently ether has been insisted upon in these cases and no operative death has occurred. Certainly if pentothal and curare or even local are to be used in a patient with history of asthma or who is having an asthmatic attack, one must be extremely cautious.

Ether

Ether still has an important place in bronchoesophagology. It is the only safe anesthetic for general anesthesia in infants. It is the anesthetic of choice in children under 10 years of age. The youngest in this series was five weeks old. It is also a safe anesthetic in elderly people. In the middle age group we use ether almost exclusively for asthmatics. Local is not necessary in these patients because adequate relaxation can be produced with ether alone. Although it takes a little more time and patience to anesthetize an adult asthmatic with ether, one does not run the risk of

TABLE V
TOTAL CASES IN WHICH ETHER WAS USED ALONE OR WITH PENTOTHAL INDUCTION

Ether Only	465
Ether and Rectal Pentothal	116
Ether and I.V. Pentothal	22
Ether, Local, and I.V. Pentothal	3
Ether and Local	9
Ether and Nitrous Oxide	1
TOTAL	616

reaction to local. Table V illustrates the various ether combinations employed.

Ether and Pentothal.—Rectal pentothal was used as an induction agent in children 116 times. It is useful where the child is apprehensive or if the procedure is being repeated on many occasions. It may be given on the ward but preferably in the anesthetic room, and is followed with ether. We had a girl, 18 months old, with tracheal stenosis following intubation for acute laryngotracheobronchitis associated with measles. She was bronchoscoped a total of 25 times over a period of several years. She was always induced with rectal pentothal and then given ether by mask. She never had fear about the procedure. Likewise a boy, two years old, with severe stricture of the esophagus due to chemical burns was esophagoscoped and dilated directly through the esophagoscope 60 times in a period of seven years.

Ether and Intravenous Pentothal.—Rarely is induction done by pentothal intravenously in children. This method is usually reserved for adults who object strenuously to the smell of ether or prefer a needle to a mask. These people are sometimes given a small amount of pentothal intravenously and then continued with ether. Intravenous pentothal was used as the induction agent for only 22 procedures. In three of these local was also used. Ether and local alone were used in only nine cases, and in one case the child was induced with nitrous oxide.

Ether not only is the safest anesthetic for asthmatics, but it also benefits them therapeutically in that it produces relaxation of the bronchi and liquefaction of the secretions, thus allowing easier removal of secretions and bronchiolar casts.

Ether by its excellent relaxation of the larynx and cricopharyngeus also facilitates removal of foreign bodies from the tracheobronchial tree and esophagus in infants and children.

SUMMARY

This report includes 4,212 bronchoesophagological procedures under general anesthesia in a 10 year period.

Intravenous pentothal was given in 3,624 instances, and ether in 616.

Local anesthesia pentothal and a muscle relaxant (a curare-like drug) was the preferred method in adults. The relaxant drug was omitted in some elderly and debilitated persons. Preoperatively morphine or pantopon was given, usually combined with atropine or scopolamine. Pontocaine was used as the topical agent until February 1952 after which time 5 per cent cyclaine was substituted. Flaxedil was also substituted for curare at this time.

Pentothal gives a pleasant induction, prevents and counteracts reactions from local agents, rarely produces postoperative nausea or vomiting, and if properly gauged the patient is usually reacting before leaving the operating room. It may be repeated many times without apprehension by the patient. It is not inflammable.

Pentothal and the relaxant must be given separately, induction must not be hurried and the patient must be at the proper depth of anesthesia and relaxation before attempting to introduce the endoscopic instrument.

Pentothal and curare are dangerous in asthmatics. The only death in this series occurred in an asthmatic person who had received these drugs.

Ether is the safest anesthetic for infants and was used routinely for children under ten. It is preferable in adults with severe emphysema, or asthma or tenaceous secretions. It may be used with pentothal as an induction agent either rectally or intravenously.

RESUMEN

Esta información corresponde a 4,212 maniobras broncoesofagológicas llevadas a cabo en diez años. En 3,624 se usó el pentotal intravenoso como anestésico general, y en 616 se usó del éter. Las drogas relajantes se omitieron en algunos ancianos y debilitados.

Preoperatoriamente se dieron morfina y pantopón, generalmente asociados a la atropina y la escopolamina. Se usó la pantocaína como tópico hasta Febrero de 1952, y a partir de entonces se substituyó por la ciclaína al 5 por ciento. Se usó también desde entonces el Flaxedil en lugar del curare.

El pentotal proporciona una inducción agradable, evita y contrarresta las reacciones a los agentes locales, rara vez produce náusea postoperatoria o vómitos y si se dosifica bien, el enfermo ya reacciona antes de abandonar la sala de operaciones.

Puede usarse muchas veces sin que el paciente manifieste aprensión. No es inflamable.

El pentotal y el relajante deben darse por separado, la inducción no debe ser apresurada y el enfermo debe ser llevado a la profundidad de anestesia apropiada así como a la relajación, ntes de introducir el instrumento endoscópico.

El pentotal con curare es peligroso en asmáticos. La única muerte en esta serie, ocurrió an un asmático que había recibido otras drogas.

El éter es el anestésico más seguro para los infantes y se usó como de rutina en los menores de diez años. Es de preferirse en los adultos con enfisema o asma o con secreciones muy espesas. Puede usarse con el pentotal como agente de inducción ya sea rectal o intravenosamente.

RESUME

L'auteur rapporte 4.212 examens broncho-oesophagologiques pratiqués sous anesthésie générale pendant une période de dix ans. Le pentothal intraveineux fut utilisé dans 3.624 cas, et l'éther dans 616 cas. On négligea la médication calmante chez certaines personnes âgées ou débilitées. Avant l'opération, on administra de la morphine ou du pantopon, généralement associé à de l'atropine ou à de la scopolamine. La pontocaine fut utilisée comme agent local jusqu'au mois de février 1952, date après laquelle la cyclaine à 5% lui fut substituée. Le flaxedil fut aussi substitué au curare à ce moment.

Le pentothal provoque un état agréable, empêche et combat les réactions des produits utilisés localement, produit rarement des nausées post-opératoires, ou des vomissements, et s'il est convenablement administré au malade, a généralement cessé son action avant que le malade ait quitté la salle d'opération. Il peut être répété plusieurs fois sans danger. Il n'est pas inflammable.

Le pentothal et les produits calmants doivent être donnés séparément, l'administration des produits doit se faire lentement, et le malade doit être suffisamment anesthésié et relaxé avant qu'on tente d'introduire l'instrument endoscopique.

Le pentothal et le curare sont dangereux chez les asthmatiques. Le seul décès dans ce groupe survint chez un asthmatique qui avait reçu d'autres médications.

L'éther est l'anesthésique le plus sûr chez les bébés, et il a été utilisé d'une façon habituelle chez les enfants de moins de dix ans. Il doit être préféré chez les adultes atteints d'emphysème sévère, d'asthme ou encombrés de sécrétions. Il peut être associé au pentothal, utilisé comme prémédication par voie rectale ou intraveineuse.

ZUSAMMENFASSUNG

Dieser Bericht hat zum Inhalt 4212 broncho-ösophageale Eingriffe unter Vollnarkose während einer Periode von 10 Jahren. Pentothal intravenös wurde in 3624 Fällen gegeben und 616 mal Äther. Das Relaxans wurde weggelassen bei einigen älteren und entkräfteten Personen. Vor dew Eingriff wurde Morphium oder Panthopon gegeben, gewöhnlich in Kombination mit Atropin oder Skopolamin. Pantocain wurde als Zeitgemässes Mittel gegeben bis Februrar 1952 und danach ersetzt durch 5% Cyclamin. Zu dieser Zeit wurde auch das Curare durch Flaxedil ersetzt.

Pentothal liefert eine angenehme Narkose-Einleitung, verhindert und bekämpft Reaktionen örtlicher Wirkstoffe, führt selten zu postoperativem Schwinder oder Erbrechen, und bei richtiger Dosierung vermag ded Patient bereits zu reagieren, ehe er den Operations-Saal verlässt. Es kann viele Male wiederholt werden ohne Abneigung des Kranken. Es ist nicht entzündbar.

Pentothal und das Relaxans müssen getrennt gegeben werden, die Einleitung der Narkose darf nicht überstürzt werden, und der Kranke muss

einen entsprechenden Grad von Schmerzunempfindlichkeit und Entspannung erreicht haben, ehe der Versuch der Einführung des endoskopischen Instrumentes unternommen wird.

Pentothal und Curare sind gefährlich bei Asthmatikern. Der einzige Todesfall in dieser Serie ereignete sich bei einem Asthmatiker, der andere Medikamente erhalten hatte.

Ather ist das sicherste Mittel Anaestetikum bei Kindern und wurde routinemässig bei Kindern unter 10 Jahren benutzt. Es ist vorzuziehen bei Erwachsenen mit schwerem Emphysem oder Asthma oder zäher Sekretbildung. Es kann zusammen auf Pentothal zur Narkose-Einleitung gebraucht werden entweder rectal oder intravenös.

REFERENCES

1 Jackson, C. and Jackson, C. L.: *Bronchoscopy, Esophagoscopy and Gastroscopy*, 3d ed. W. B. Saunders Co., Philadelphia, 1934.

2 Jackson, C. and Jackson, C. L.: *Bronchoesophagology*. W. B. Saunders Co., Philadelphia, 1950.

3 Rubin, E. H. and Rubin, M.: *Diseases of the Chest*. W. B. Saunders Co., Philadelphia, 1947.

4 Benedict, E. B.: *Endoscopy*. The Williams and Wilkins Co., Baltimore, 1951.

5 Thomson, St. C. and Negis, V. E.: *Dis. Nose and Throat*, fifth ed. Appleton-Century-Crofts, Inc., New York.

6 Pullen, R. L.: *Pulmonary Diseases*. Lea and Febiger, Philadelphia, 1955.

7 Cassels, W. H. and Holinger, P. H.: "Points of Mutual Interest in Bronchology and Anesthesiology," *Ann. Otol., Rhinol. and Laryngol.*, 55:638, 1946.

8 Holinger, P. H.: "Progress in Esophagology," *Arch. Otol.*, 47:119, 1948.

9 Thomas, J. W. and Fenton, M. M.: "Fatalities and Constitutional Reactions Following the Use of Pontocaine," *Jour. Aller.*, 14:145, 1943.

10 Lierle, D. M.: "Topical and Infiltration Anesthesia," *Transactions American Academy of Ophthalmology and Otolaryngology*, p. 288-293 (March-April), 1949.

11 Weisel, W. and Tella, R. A.: "Reaction of Tetracaine (Pontocaine) Used as Topical Anesthetic in Bronchoscopy, Study of 1,000 Cases," *J.A.M.A.*, 147:218, 1951.

12 Schoemperlen, C. B.: "Diagnostic Bronchoscopy," *C.M.A.J.*, 60:11, 1949.

13 Fatti, L. and Morton, H. J. V.: "Pentothal Anaesthesia in Bronchoscopy," *Lancet*, 1:597, 1944.

14 Lorhan, P. H. and Roberts, S.: "'Intocostrin'—Pentothal Sodium Anesthesia for Bronchoscopy and Laryngoscopy," *Arch. Otol.*, 46:789, 1947.

15 Adams, R. C.: "General Anesthesia," *Transactions American Academy of Ophthalmology and Otolaryngology*, p. 299-302 (March-April), 1949.

16 Pembleton, W. E. and Vinson, P. P.: "Anesthesia Peroral Endoscopy, Especially General Anesthesia in Esophagoscopy and Gastroscopy," *Arch. Otol.*, 50:561, 1949.

17 Butt, W. A. and Boys, H. W.: "Anaesthesia for Bronchoscopy and Oesophagoscopy," *Can. Med. Assoc. J.*, 60:62, 1949.

18 Scharfe, E. E.: "Anaesthesia for Peroral Endoscopy," *Can. Med. Assoc. J.*, 65:134, 1951.

19 Ament, R. and Meyers, H.: "Thiopental with Succinylcholine and Topically Applied Tetracaine. A More Ideal Anesthetic for Peroral Endoscopy," *A.M.A. Arch. Otol.*, 57:405, 1953.

20 MacIntosh, R. R.: "Anaesthesia for Bronchoscopy," *Anaesthesia*, 9:77, 1954.

21 Shane, S. M. and Ashman, H.: "A Method of General Anesthesia for Bronchoscopy and Bronchography," *Arch. Otol.*, 62:319, 1955.

22 Heatly, C. A.: "Practical Consideration of Anesthesia in Bronchoesophagology," *N. Y. St. J. Med.*, 56:367, 1956.

23 Tremble, G. E. and Baxter, J. A.: "Anaesthesia in Otolaryngology," *Can. Med. Assoc. J.*, 75:25, 1956.

24 Orkin, L. R. and Rovenstine, E. A.: "Topical Anesthesia with Hexylcaine (Cyclaine) for Major Endoscopic Procedures," *J.A.M.A.*, 160:1465, 1956.

25 Hunter, A. R.: "Antidotes to Curarizing Drugs," *Can. Med. Assoc. J.*, 74:892, 1956.

Blood Dyscrasias
Associated with Antituberculosis and Combined Antituberculosis-Tranquilizing Chemotherapy

THOMAS WOROBEC, M.D., F.C.C.P.
Downey, Illinois

Introduction

The dynamics of chemotherapeutic drugs involve complex mechanisms in drug-parasite-host relationships. An increasing number of publications report severe blood dyscrasias induced by chlorpromazine and chloramphenicol, but few published reports incriminate antituberculosis drugs. Modern treatment of neuropsychiatric-tuberculous patients, including antituberculosis chemotherapy, surgical intervention, psychotherapy and tranquilizing drugs, has resulted in a gratifying picture on neuropsychiatric-tuberculosis wards. Arrest, inactivation, or removal of tuberculous lesions has been reflected in a dramatically improved neuropsychiatric condition in many patients. Prolonged antituberculous chemotherapy and the increasing use of tranquilizing drugs in treating neuropsychiatric and emotionally unstable tuberculous patients may cause serious problems.

The purpose of this publication is to report two cases (one a case of leukemoid reaction, hepatitis and dermatitis while on streptomycin and isoniazid, and the other a case of fatal agranulocytosis with confluent pleuropneumonia, on para-amino salicylic acid, isoniazid and chlorpromazine). Also to make a preliminary report of incidence of transient leucopenia, fluctuating leucocyte count and changes in differential count, based on clinical observation in cooperation with Dr. W. H. Newton.

Case 1: C. C. B. This 31 year old veteran was admitted to the neuropsychiatric-tuberculosis service, Veterans Administration Hospital, Downey, Illinois, on October 31, 1954. He had been continuously hospitalized elsewhere since 1949 for schizophrenic reaction, chronic, severe. Family History: Not remarkable. Past History: Syphilis, primary, in September 1944, treated; acute tonsillitis in December 1944; epididymitis, acute, non-venereal, in February 1945. The admission physical examination was within normal limits except for signs referable to the chest. X-ray films showed infiltration with cavitation in the upper lobe of the right lung and an infiltrate in the apical segment of the upper lobe of the left lung. Gastric washings contained acid fast bacilli on culture. The organisms were sensitive to streptomycin, para-amino-salicylic acid and isoniazid. Admission serology, hematology, blood chemistry and urinalysis were normal except for thymol turbidity test, 2 units.

On December 29, 1954 1 gram of streptomycin twice weekly, and 4 grams of para-amino salicylic acid three times daily, were started. Tranquilizing drugs were not given. Routine laboratory follow-up studies remained unchanged. On January 27, 1955, the 88th hospital day and 30th day of chemotherapy, he developed chills, fever of 103.4° F., nausea and malaise. Physical examination, except for moderate pharyngeal inflammation, was normal. Tetracycline, 1.0 gram daily, and penicillin, 600,000 units daily, were given but a remittent type of fever spiking to 104.4° F. persisted and he became increasingly toxic. On February 7, 1955, 12 days after onset of this acute episode, he reacted with increased nausea, emesis and pain in the right upper abdominal quadrant. Other new signs included mild swelling of the soft tissues of the orbit bilaterally, generalized erythematous dermatitis, generalized lymphadenopathy, and palpable, tender liver. The pharynx remained unchanged. The lack of response to broad spectrum antibiotics, sterile cultures for B hemolytic streptococci, the clinical

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Chief, NP-TB Service, Veterans Administration Hospital.

picture and laboratory findings were all considered compatible with hypersensitivity reaction due to drugs. Therefore, SM and PAS were stopped. Slowly decreasing temperature followed. However, he appeared more toxic. Tetracycline and penicillin were discontinued on the following day but low grade fever without spiking continued. On February 8, 1955 icterus was noted in the sclerae. Laboratory findings that day were: Urinalysis—albumin 3+, urobilinogen quantitive 1:160 dilution. Hemogram—white blood cell count 25,000, 80 per cent neutrophils, 18 per cent lymphocytes, and 2 per cent eosinophils, red blood cell count 3,780,000, hemoglobin 12 grams, color index 1.02, mild basophillic stippling, malaria negative, sedimentation rate 3 mm. per hour, icteric index 44.2 units. Cephalin flocculation was 3+ in 48 hours, thymol turbidity 6.25 units, fasting blood sugar 106 mg. per cent, NPN and urea nitrogen not elevated.

Liver function tests and urinalysis showed marked hepatocellular impairment. On February 11, 1955, the hemogram showed WBC 95,000 24 per cent neutrophils, 39 per cent lymphocytes, 29 per cent eosinophils, 8 per cent monocytes, a blood picture resembling a leukemoid reaction with enlarged lymphocytes. This report was re-checked and confirmed by the chief of the laboratory service, Dr. M. A. Jacobson. Bone marrow examination, the electrophoretic protein pattern, and other immunochemical studies were requested but were not available at the time.

The initial leucocytosis with 80 per cent neutrophils was considered a response to tissue damage, the subsequent lymphocytosis as a lymphoid or reticuloendothelial tissue response, and eosinophilia was compatible with an allergic state, giving a clinical picture strongly suggestive of reduction in circulating antibodies. Empirically he was given 0.15 cc. per kilo of gamma globulin intramuscularly. The next day he appeared less toxic and subsequently improved slowly. Infectious mononucleosis was considered as an alternate explanation of the rather bizarre sequence of events. Heterophile antibody test of Paul-Bunnell was reported positive in 1:28 dilution on February 14, 1955, in 1:56 dilution on February 16, 1955, but was negative on February 25, 1955. This diagnosis, therefore, was not proved.

Hemogram on February 14, 1955 showed white blood cell count 28,000, 69 per cent lymphocytes, 31 per cent neutrophils. ECG on February 15, 1955 was read as normal. A small test dose of 250 mg. streptomycin resulted in reaction consisting of chills, fever and skin rash. A test dose of 3 grams of rezipas resulted in nausea, malaise, leucocytosis and slightly abnormal liver function tests. On April 18, 1955 the total protein was 8.24, A/G ratio .585, A/B ratio 3.10, albumin 36.90 per cent, alpha 1, 6.03 per cent, alpha 2, 9.30 per cent, beta 11.90, gamma globulin 35.82 per cent.

The anti-streptolysin titer was 1:500 on February 25, 1955. On recheck April 18, 1955 by the Naval Medical Research Laboratory, Great Lakes, Illinois, the anti-streptolysin titer was 1:600. These findings do not necessarily incriminate the streptococcus as a direct etiologic agent and may have indicated previous streptococcic infection.

Since February 15, 1955 symptoms, signs and laboratory reports have shown steady improvement. He became asymptomatic and by the end of May all laboratory findings returned essentially to normal values. Following recovery there was no radiologic evidence of progression of the bilateral tuberculous lesions. Antituberculosis chemotherapy consisting of INH alone was restarted on September 14, 1955, with slowly increasing doses to 100 mg. three times daily by September 26, 1955. Pyrazinamide, 1.5 grams daily, was added April 10, 1956 without untoward reaction and has been continued. Viomycin was tried but caused recurrence of fever, malaise and leucocytosis. The right upper lobe was resected on May 15, 1956, when penicillin and tetracycline were tolerated without difficulty. His postoperative course was protracted, the remaining lobes expanding slowly and with gradual absorption of fluid. Following surgery cultures were negative for acid fast bacilli until recently. Planigraphic studies show evidence of possible cavitation in the left upper lobe. The tubercle bacilli are sensitive to SM, PAS and INH. Segmental resection on the left side is being considered.

Case 2: J. D., This 30 year old white single man, was admitted to the neuropsychiatric-tuberculosis service, Veterans Administration Hospital, Downey, by transfer from Fitzsimons Army Hospital September 30, 1955. He had first been hospitalized at Camp Gordon on January 3, 1955 for an acute psychiatric disorder. Routine chest x-ray film showed an infiltrate in the left apical region and he was transferred to Fitzsimons on February 11, where he reacted to tuberculin but not to coccidioidin and histoplasmin. Three gastric cultures were negative for acidfast bacilli. He had been given SM, 1 gram every third day, and INH, 300 mg. daily. In addition he had received 30 electroshock treatments, from February 8 to March 30, 1955, and 33 insulin shock treatments, from April 13 to May 27, with some improvement in his mental condition.

On admission to the hospital the physical examination was within normal limits. His height was 72", weight 149 pounds, blood pressure 118/78. Because of mental confusion, it was difficult to obtain a clear picture of his past and family history other than that he had come to the United States from Yugoslavia after the second world war.

Hospital Course: Antituberculosis chemotherapy consisting of SM, 1 gram twice weekly, and INH, 300 mg. daily, was continued until December 1955, when he refused SM injections and the regimen was changed to PAS, 12 grams daily, and INH, 300 mg. daily. Serology, blood chemistry and urinalysis were normal. The white blood cell count was 5,200, with 65 per cent neutrophils, 33 per cent lymphocytes, 2 per cent monocytes. The hemoglobin was 14.5 grams, color index 1.0, sedimentation rate 1 mm. per hour. Liver function tests on October 4, 1955 showed cephalin flocculation 2+ in 48 hours, thymol turbidity 3.00 units. BSP test on January 4, 1956 showed 1.0 per cent retention in 45 minutes. The pulmonary condition was evaluated at the medical staff conference and on February 20, 1956 the diagnosis of tuberculosis, pulmonary, chronic, minimal, active, was changed to minimal, active, improved.

On December 6, 1955 he was placed on chlorpromazine, 50 mg. twice daily. On May 7, 1956 he eloped from the recreation room and subsequent to his return became an eating problem. In two weeks he lost six pounds of body weight and, therefore, supplemental tube feeding was started. On May 15, 1956 cephalin flocculation was 2+ in 48 hours, thymol turbidity 1.5 units. Hemogram on May 16, 1956 showed 6,800 white blood cells with 61 per cent neutrophils, 39 per cent lymphocytes, hemoglobin 14 grams 91 per cent, color index 0.96, sedimentation rate 4 mm. per hour.

On May 28, 1956 at 2:30 P.M. after 200 cc. of supplemental nourishment had been given, he had emesis. Tube feeding was stopped, and no side effect was noted the remainder of the day. His temperature was 98° F. orally, pulse 86, respiration 18, blood pressure 100/74, with no coughing spells. On May 29, 1956 at 8 a.m. he appeared acutely ill, with abrupt onset of chills, pounding pulse 114, temperature 102.6° F., respiration 28, blood pressure 110/70. The mouth and throat showed slight congestion but no ulceration. There were suppressed breath sounds over the lower half of the right lung and, after a few hours, fine rales were heard and impaired percussion elicited. He developed non-productive painful coughing spells but no other symptom or sign. Emergency leucocyte and differential count revealed 1,250 white blood cells with 25 per cent neutrophils, 68 per cent lymphocytes, 7 per cent monocytes. Sputum for bacteriologic studies could not be secured. Portable chest x-ray film showed pneumonic infiltration in the right lower lung field. Our clinical impression was (1) granulocytopenia due to drug hypersensitivity, (2) right lower lobe pneumonia, probably from inspiration of vomitus on previous day. Chlorpromazine, PAS and INH were discontinued and, in order to combat what appeared to be severe pulmonary infection, crysticillin, 600,000 units q 12 hours, and tetracycline, initial dose 500 mg. with 250 mg. q 4 hours were started. Liver extract, 20 mg. USP 1 q 12 hours, was given in the hope of stimulating the bone marrow. His temperature rose gradually to 104.2° F. At 9 p.m. his pulse was 126, respiration 30. At 10:30 p.m. his temperature was 105.2° F. and he developed signs of hypotension with dyspnea, cyanosis and repeated emesis. However, he was able to take fluids and liquid nourishment orally until the end. Symptoms and signs of circulatory failure attributed to bacterial toxemia were progressive. On May 30, 1956 at 7:30 a.m. oxygen was started. By 8:30 his temperature was 106°, followed by a rapid drop, Cheyne-Stokes respiration and vascular collapse. He expired at 9:05 a.m.

Necropsy revealed moderate fibrosis with a large number of congested blood vessels resembling an angiomatous pattern in the apex of the lung. Large areas of extravasated blood were also present. Small accumulations of lymphocytes were seen. The adjacent alveolar tissue contained edema fluid with large numbers of bacteria. *Other areas of the lung* disclosed a pneumonia-like appearance. The alveoli were filled with round cells, only a few of which were polymorphonuclear leukocytes, others resembled histiocytes. Many cells of the exudate revealed coarse granula in their cytoplasma. Red blood cells were also present in the alveolar spaces, variable in size and with a more bluish appearance in contrast with the erythrocytes inside blood vessels. The alveolar wall as well as the other lung tissue did not stain normally and had an appearance resembing that found in infarcted areas (Figures 1A, 1B). Small fat droplets were seen in the liver cells, but there was no other finding indicating toxic damage. There was moderate passive congestion of spleen pulpa, no finding indicating increased hemolysis. Moderate passive congestion was present in the kidneys and occasional minimal transudation in Bowman's capsules. The heart, adrenals, prostate and brain showed no histopathological change. Bone marrow smear showed degeneration of myeloid cells while myeloblasts were aplastic.

Comment

Other published reports and our case of leukemoid reaction have presented various bizarre features. Attempts to explain the mechanism of leukemoid reactions have led to the following theories: (1) Stimulation of the bone marrow, (2) Antigen-antibody reaction, (3) Infection, or (4) Mechanically by ectopic hemopoieses secondary to prolonged demand on the blood-forming organs.

In our case of leukemoid reaction with hepatitis and dermatitis, we feel that both streptomycin and PAS were injurious to the blood-forming organs. Attempts to resume treatment with the incriminated drugs were unsuccessful because of the patient's intolerance. His reaction to viomycin may be explained by cross-reaction. We regret giving gamma globulin empirically without awaiting results of the electro-phoretic protein pattern, bone marrow and lymph node biopsy studies, but the toxic condition and resulting improvement may justify our decision.

In the case, granulocytopenia with secondary confluent pleuropneumonia, all three drugs (chlorpromazine, para amino salicylic acid and isoniazid) may be implicated. Because of the rapidly progressive course of only 26 hours, it could not be determined which drug caused the irreversible damage in the bone marrow. Experimental granulocytopenia in varying degrees has been produced with the use of antileucocytic serum in vitro and in vivo (S. Moeschlin, H. Myer, L. G. Israels and E. Tarr). The presence of leucoagglutinins in serum of leucopenic patients has been reported

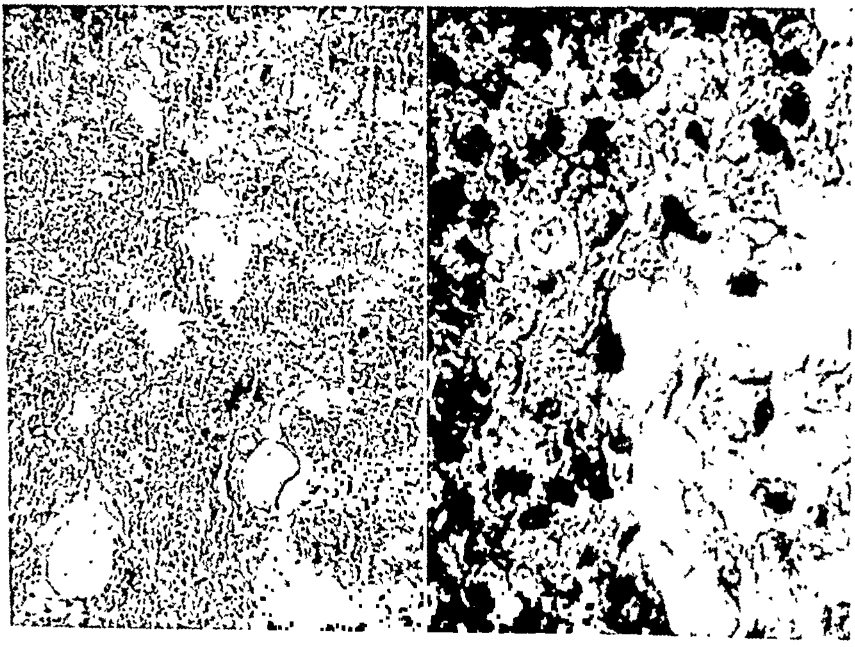

FIGURE 1A FIGURE 1B

with fatal outcome. Probably they are antibodies acting on antigens carried by human leucocytes. Results of more recent studies imply that leucopenia is produced by agglutination of leucocytes in peripheral circulation with subsequent removal of leucocytes in the lung capillaries.

The anaphylactoid course of pulmonary infection and failure of penicillin, 600,000 units every 12 hours with tetracycline, resulted because of the

INCIDENCE OF MILD FLUCTUATING BLOOD REACTION, Patients at VA Hospital, Downey, Illinois, Neuropsychiatric-Tuberculosis Service (251 bed capacity) during 1956.

Patients treated (total)	337
Patients receiving anti-tuberculous or tranquilizing drugs, or both	229
Total incidence, aberrant blood findings (excluding surgical cases, transient illnesses, and two cases with severe reactions, described elsewhere in this report	55
Leukopenia (below 5,000 WBC)	17
Leukocytosis (above 10,000)	30
Reversed neutrophil-lymphocyte differential count	8
Returned to normal, one to four weeks, following drug discontinuance	55

TABLE I

LEUKOPENIA FINDINGS—17 CASES

DRUG REGIMENS At time of reaction					LABORATORY FINDINGS				SYSTEMIC
					Prior	At Time			
	Anti-TB (Mos. prior)		Tranquilizing (Mos. prior)		Cephalin floc. 48 hrs.	Thymol turb. units	Cephalin floc.	Thymol turb. units	Temp. elevation Dermatitis GI symptoms Dyspnea
2	SM-PAS	33 19	Frenquel	12 5	1+ 2+	3.5 3.5	0* 1	0* 2	GI, emesis prior dermatitis
1	SM-INH	24	Serpasil	17	0	0	1+	1.5	
1	SM-INH	20	Thorazine	10	0	0	1+	.5	Temp. to 100.2°
4	SM-INH	17 2 42 39	None		0 4+ 0 0	1.5 3.5 1.74 2.5	0 0 0 0	1.5 3.0 2.5 2.5	dermatitis (SM)
1	SM-PAS & INH	4	Sparine	3	2+	1.5	trace	1.5	severe dermatitis
2	SM-PAS & INH	19 5			1+ trace	2.0 .2	0* 1+	0* 2.82	
1	PZA-INH	4	Sparine	3	0	1.5	0	1.5	
1	SM	1	None		2+	2.0	1+	2.5	
1	None		Atarax	2	unknown	unk.	3+	3.5	
1	None		Thorazine	11	Icteric index	6.5U	unk.	unk.	
1	None		None		0	2.5	unk.	unk.	
1	SM-INH	9	Frenquel	8	0	0	4+	5.37	hepatitis, with icterus

*Temporarily negative only.

inability of the body to mobilize its defenses, a sequel of the destruction of the leucocytes, essential elements in the body's defensive mechanisms. The often reported beneficial effect of the combined use of ACTH or cortisone in addition to the antituberculosis drugs in severe infections and drug-hypersensitivity reactions in suppressing not only fever but neutrophilia was not justified in our case in patient with pulmonary tuberculosis without coverage of antituberculosis drugs. Whether blood transfusion, which was planned for the next day, would have helped to correct the circulatory failure seems doubtful.

For reported incidence of transient, mild, fluctuating blood dyscrasias, leucopenia, shift in differential count and leucocytosis among our neuropsychiatric patients (see Table I). The clinical observations were undertaken with the purpose of watching for signs of early mild reactions, in order to prevent the development of more severe toxic blood dyscrasias. The preliminary impression, based on current clinical observations, does not implicate specifically one single or combination of drugs for increased incidence. The observed fluctuation of the blood picture may be explained in the light of present concepts by enzymatic interference of most of the drugs in drug-parasite-host relationships. Immediate discontinuation of the offending drug or drugs brought reversal of the abnormal blood picture in one to four weeks. The greater incidence of mild blood dyscrasias among our patients who are on chemotherapy may be understood by (1) the older age distribution of our patients, 73 per cent of whom are over 50, and 60 per cent over 60 years of age, (2) the long period of hospitalization for neuropsychiatric conditions, tuberculosis, or both, (3) coexisting organic diseases such as chronic alcoholism with liver damage, (4) various previous drug regimens, insulin coma or electroconvulsive therapy. We have no reason to believe that neuropsychiatric-tuberculous patients, as such, are constitutionally more susceptible to adverse drug reactions than other patients with tuberculosis.

It appears of interest to note that in some cases, when the suspected drug or drugs were resumed with supplemental vitamins as indicated, the blood picture remained normal, other side effects such as skin rashes and gastric intolerance disappeared, and well-being improved. These observations are in agreement that most chemotherapeutic agents may be considered antimetabolites. Our clinical observations for evaluating supplemental use of vitamins to correct a clinically suspected deficiency have been favorable and in accord with published results elsewhere.

SUMMARY

Two cases of hypersensitivity reaction to antituberculosis drugs are reported. With streptomycin and para-amino salicylic acid, one presented spiking fever, generalized erythematous dermatitis, lymphadenopathy, hepatitis with icterus, and a blood picture resembling infectious mononucleosis with leukemoid-lymphocytic reaction. Following desensitizing doses of streptomycin and PAS, the patient again showed evidence of toxicity to these drugs and also apparent cross-reaction with viomycin.

He tolerated isoniazid, pyrazinamide, and the broad-spectrum antibiotics. The other with PAS, isoniazid and chlorpromazine developed granulocytopenia, pleuropneumonia, and rapidly progressive circulatory failure attributed to bacterial toxemia, with no response to combined broad-spectrum antibiotics. The responsible drug or drugs could not be determined because of the rapidly fatal termination 26 hours after the onset of the acute illness.

Preliminary clinical observation does not specifically implicate one single or combination of drugs. Our clinical experience in the evaluation of the supplemental use of vitamins in correcting clinically suspected deficiencies has been favorable when a drug suspected of causing toxicity was resumed and apparently well tolerated.

RESUMEN

Se relatan dos casos de hipersensibilidad a las drogas antituberculosas. El primer enfermo, tratado con estreptomicina y PAS presenta un extraño cuadro clínico caracterizado por fiebre en agujas, dermatitis eritematosa diseminada, linfadenopatía, hepatitis ictérica y fórmula sanguínea parecida a la mononucleosis infecciosa con reacción leucemoide-linfocítica. Después de tratarse con dosis desensibilizantes de estreptomicina y PAS el enfermo mostró nuevamente evidencias de toxicidad a esas drogas así como reacción cruzada aparente a la viomicina. Tolera isoniacida, pirazinamida y los antibióticos de amplio espectro.

El segundo caso fué tratado con PAS, isoniacida y chloropromazina. La toxicidad se manifestó por una reacción anafilactoide con principio repentino de granulocitopenia, pleuroneumonía, y desfallecimiento progresivo y rápido circulatorio atribuído a toxemia bacteriana sin res puesta a los antibióticos de amplio espectro. No se pudo determinar cual era la droga o las drogas responsables debido a la terminación fatal des pués de 26 horas del principio de la enfermedad aguda.

La frecuencia de discracias sanguíneas moderadas aparentes, entre los enfermos neuropsiquiátricos tratados por drogas antituberculosas así como drogas tranquilizantes durante el año pasado, es objeto de informaciòn. La varación al aparecer mayor de fluctuaciones en los cuadros sanguíneos en 54 enfermos de un total de 229 bajo varios regímenes de drogas puede explicarse tal vez por: (1) edad mayor de los trastornos orgánicos coexistentes, (2) tratamiento prolongado con tales procedimientos o como el coma insulínico y los electrochoques. Las observaciones clínicas preliminares no implican de manera especial a una simple droga o combinación de drogas. Nuestra experiencia clínica en la valuación de las vitaminas para corregir las deficiencias sospechadas clínicamente ha sido favorable cuando la droga sospechosa de toxicidad se ha vuelto a emplear y es entonces bien tolerada. Esto está de acuerdo con otras informaciones antes publicadas.

Los resultados de los estudios publicados recientemente para aclarar los mecanismos fundamentales de las dicrasias sanguíneas causadas por las drogas antituberculosas, las tranquilizantes o las combinaciones se discuten aquí y se recalca la necesidad de hacer una estimación cuida dosa

de la dinámica se las relaciones droga-parásito-huésped antes de usar las drogas. La posibilidad de efectos desagradables complicando la quimoterapia en los individuos susceptibles, se hace resaltar.

RESUME

L'auteur rapporte deux cas d'hypersensibilité aux médications antituberculeuses. Le premier malade, traité par la streptomycine et le P.A.S. présente une évolution clinique bizarre, caractérisée par une fièvre hectique, une dermatite érythémateuse généralisée, des adénopathies, une hépatite avec ictère, et une atteinte sanguine ressemblant à une mononucléose avec réaction lmphocytique leucémoïde. Après essai de désensibilisation à la streptomycine et au P.A.S., le malade donna de nouveau la preuve d'une intoxication due à ces médications et manifesta en outre une réaction croisée évidente à la viomycine. Il toléra l'isoniazide, la pyrazinamide et les antibiotiques de seconde zone.

Le deuxième cas fut traité par le P.A.S., l'isoniazide, et la chlorpromazine. La toxicité manifestée était de type anaphylactique caractérisée par une apparition soudaine d'agranulocytose, de pleuropneumonie, et une atteinte circulatoire progressive, attribuée à la toxémie bactérienne, qui ne répondit pas aux associations d'antibiotiques mineurs. La ou les médications responsables ne purent être précisées à cause de la rapidité de l'évolution qui se montra fatale 26 heures après l'apparition des manifestations.

L'auteur rapporte l'apparition de manifestations sanguines, faibles et transitoires chez les malades de neuropsychiatrie, traités par les médications antituberculeuses et calmantes au cours de l'année. La fréquence de fluctuation apparemment plus grande dans les tableaux sanguins de 54 malades sur un total de 229 malades soumis à des régimes médicamenteux différents, peut être expliquée par 1) l'ancienneté des troubles organiques coexistants; 2) un traitement prolongé associé à des moyens tels que le coma insulinique, et la thérapeutique électroconvulsive.

ZUSAMMENFASSUNG

Bericht über 2 Fälle von Überempfindlichkeits-Reaktion gegen antituberkulöse Heilmittel.

Der 1. Patient wurde mit Streptomycin und PAS behandelt und bietet einen bizarren klinischen Verlauf, charakterisiert durch zackenförmigen Fieberverlauf, generalisierte erythematöse Dermatitis, Lymphadenophatie, Hepatitis mit Gelbsucht und einem Blutbild, ähnlich der infektiösen Mononucleose mit leukaemisch-lymphozitärer Reaktion. Im Anschlub an desensibilisierender Dosen von Streptomycin und PAS bietet der Patient wieder das Bild der Toxizität auf dieses Medikament, so wie auch eine augenscheinliche Überkreuzreaktion mit Viomycin. Er vertrug INH, Pyracinamid und die Breitwandspektrum Antibiotika.

Der 2. Fall wurde behandelt mit PAS, INH und Chlorpromacin. Seine Toxizität manifestierte sich als ein anaphyklaktischer Reaktionstyp gekennzeichnet durch plötzliches Auftreten einer Granalocytopenie, Pleuropneumonie und rasch fortschreitendes Kreislaufsversagen als Ausdruck

bakterieller Toxamie mit fehlender Antwort auf kombinierte Breitwandspektrum Antibiotika. Das oder die verantwortlichen Heilmittel konnten nicht ermittelt werden wegen des raschen tötlichen Ablaufes 26 Stunden nach dem Beginn der akuten Erkrankung.

Bericht über das Auftreten von offenbar flüchtiger, leichter Dyscrasie des Blutes unter neuropsychiatrischen Patienten während der Behandlung mit antituberkulösen sowie mit beruhigend wirkenden Arzneimitteln im Verlauf des vergangenen Jahres. Die scheinbar grössere Häufigkeit des Schwankens des Blutbildes bei 54 Kranken von insgesamt 229 Kranken unter verscheidenen Arzneimittelkombinationen kann erklärt werden 1) durch die erhöhte Altersverteilung gleichzeitig vorkommender organischer Störungen, 2) durch die verlängerte Behandlung kombiniert mit Insulin-, Koma-, Elekro-Schockbehandlung. Die bisherige klinische Beobachtung lässt kein einzelnes Medikament oder eine Medikamenten-Kombination besonders beteiligt sein. Unsere klinische Erfahrung bei der Auswertung der ergänzenden Anwendung von Vitaminen zur Korrektur klinisch vermuteter Mangelerscheinugen waren günstig, wenn ein Medikament, dessen toxische Wirkung vermutet wurde, wieder verordnet und augenscheinlich gut vertragen wurde. Dies stimmt überein mit früher veröffentlichten Berichten.

Besprechung der Resultate der neueren Literatur über Untersuchungen zur Aufklärung der grundlegenden Mechanismen der Blutzersetzung entstanden durch Antituberkulöse Mittel, Beruhigungsmittel oder kombinierte Chemotheraphie; hervorgehoben wird die Notwendigkeit vorsichtiger Erfassung des Kräftespieles in der Beziehung zwischen Medikament, Erreger und Wirt. Betont wird die Möglichkeit ungünstigen, komplizierender Wirkungen der Chemotheraphie bei empfindlichen Induvidien.

BIBLIOGRAPHY

Dausset, J. and Menna, A.: "Presence of Leucoagglutinins in Serum of Three Leukopenic Patients," *Sang. Paris,* 24:410, 1953.
Moeschlin, S., Meyer, H., Israels, L. G. and Tarr, G. E.: "Experimental Agranulocytosis," *Acta Haemat.*, 11:73, 1954.
Dameshek, W.: "Hemotoxic Reactions to Drugs," *Postgraduate Medicine*, 16:369, 1954.
Schwartz, R. S. and Hass, W. K.: "Leucoagglutinins in Agranulocytosis," *A.M.A. Arch. Med.*, 95:863, 1955.
Mahrer, R. A. and Maret, R.: "Agranulocytosis Complicating PAS and Streptomycin Therapy," *U. S. Armed Forces M. J.*, 6:1193, 1955.
Hilts, S. V. and Shaw, C. C.: "Leukemoid Blood Reactions," *New England J. Med.*, 249:434, 1953.
Friedman, E.: "Reactions to Para-Amino Salicylic Acid," *Am. Rev. Tuberc.*, 72:833, 1955.
Lichtenstein, M. R. and Cannemeyer, W.: "Severe Para-Amino Salicylic Acid Hypersensitivity Simulating Mononucleosis or Hepatitis," *J.A.M.A.*, 152:606, 1953.
Steininger, W. J., Klopfenstein, M. D. and Woodruff, C. E.: "Fatal Allergic Reaction to Para-Amino Salicylic Acid," *Am. Rev. Tuberc.*, 69:451, 1954.
Biehl, J. P. and Nimitz, H. J.: "Studies on the Use of a High Dose of Isoniazid," *Am. Rev. Tuberc.,* 70:430, 1954.
Hall, W. H. and Gold, D.: "Shock Associated with Bacteremia," *A.M.A. Arch. Int. Med.*, 96:403, 1955.
Hansen, J. E. and Cleve, E. A.: "Fatal Hypersensitivity to PAS and Streptomycin," *Dis. Chest,* 28:577, 1955.
Bulley, K. G.: "Near-Fatal Shock From PAS Followed by Guillain-Barres Syndrome," *Am. Rev. Tuberc.,* 69:455, 1954.

SECTION ON CARDIOVASCULAR DISEASES

Experiences with Myocardial Revascularization By Division of the Internal Mammary Arteries

ROBERT P. GLOVER, M.D., F.C.C.P. and J. RODERICK KITCHELL, M.D.
with
ROBERT H. KYLE, M.D., JULIO C. DAVILA, M.D. and ROBERT G. TROUT, M.D.
Philadelphia, Pennsylvania

Coronary arterial disease holds the dubious distinction of being the major cause of death and disability in the field of cardiac disorders. Its prevalence seems paradoxically to be increasing despite mounting efforts to modify its ravaging but insidious course. Basically, the offending lesion is that of arteriosclerotic vascular degeneration with its resultant gradual or sudden occlusion of portions of the arterial tree depriving the myocardium of its only source of sustenance. Although inroads have been made toward the modification of this sclerotic process by metabolic means, the ultimate solution seems remote at the moment. In the interim both physician and surgeon have attempted to improve myocardial vascularity, despite the natural progression of occlusive changes, by augmenting its diminished blood supply from neighboring vascular structures or by redistribution of myocardial blood from unaffected to affected areas.

In 1939 at the suggestion of Fieschi[1] in Italy, Zoja and Cesa-Bianchi ligated the internal mammary arteries of a patient who for some years had suffered from repeated myocardial infarcts. The operation was performed under local anesthesia and the patient enjoyed an excellent postoperative course. To quote Fieschi—"The patient, after two years, is still alive and has had no further acute attacks of infarction." This operation was the culmination of Fieschi's rather modest attempts to amplify known anatomic demonstrations of the naturally occurring communications found between the ramifications of the internal mammary arterial bed and the coronary circulation. Previously he had been able to trace, by radio-opaque injections, vascular channels from the internal mammary artery through its pericardiophrenic branch into a few periaortic and peripulmonary arterial rami. It was his hypothesis that the coronary arterial circulation

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From the Departments of Thoracic and Cardiac Surgery, and Cardiology, The Presbyterian Hospital; Fitzgerald Mercy and Lankenau Hospitals; The Thoracic and Cardiovascular Research Laboratory at Presbyterian Hospital; The Glover Clinic.

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might be favorably influenced by creating hypertension in the circulatory collateral of the mammary arteries by occluding these vessels in the second intercostal space. Indifference on the part of his professional contemporaries prevented expansion of this effort just as similar apathy has impeded the enthusiasm of most investigators throughout the world regardless of their field of endeavor.

In 1955, Battezzati, Tagliaferro and DeMarchi[1] amplified the work of Fieschi and reported the results of their anatomico-surgical research both experimental and clinical. In cadavers they injected methylene blue and India ink at the level of the second intercostal space into a segment of the internal mammary artery containing the origin of the pericardiophrenic artery after occlusion of the mammary at the subclavian artery. Excellent mapping of the vascular network within the parietal pericardium was obtained and on occasion the dye could be seen in the vascular rami of the myocardium and epicardial fat. The same but more complete and detailed findings were obtained in dogs.

Eleven patients, suffering from angina pectoris caused by coronary sclerosis, were subjected to internal mammary arterial ligation by them. In each the anginal syndrome was abolished and remained so even after the patient had returned to normal activity. In addition, the signs of myocardial insufficiency particularly dyspnea disappeared in most of those in whom it was present, as did the electrocardiographic tracings of myocardial ischemia and the ballistocardiographic recordings were modified favorably in eight of the 11. In an addendum 14 additional patients obtained similar clinical and objective improvement.

This highly favorable report stimulated the authors to repeat these studies and to observe at close range the phenomena which had presented itself to the Italian workers. It must be readily admitted that considerable skepticism as to the efficacy of such findings and results was entertained. Even though anatomical channels between the internal mammary and coronary arterial systems existed, it seemed unlikely physiologically that a sufficiently increased vascular flow between the two could be obtained by such means. On the other hand if such an innocuous procedure, surgically speaking, could result in even a portion of the reported findings, then surely a contribution of considerable magnitude was at hand. Further, the realization that for its success this method might call into play and enhance naturally existing channels which the body itself employs under stress and stimulus made this investigation doubly attractive.

Anatomical Background

As early as 1880 Langer[2] pointed out that the vascular system of the heart was not an independent circulation. He observed the vasa propria of the heart (arterial and venous) to anastomose extensively with the vessels of the pericardium, the bronchial vessels and the diaphragm via the vasa vasorum of the great cardiac vessels. He stated that these extracardiac coronary anastomoses made it possible to feed the heart collaterally after the obstruction of a main coronary branch.

Gross,[3] in 1921, confirmed this earlier work by showing distinct connections between the coronary arteries and the vessels of the parietal pericardium. He further commented upon the development of the rami telae adipose with advancing age with or without the stimulus of disease within the coronary arterial pathways.

In 1932, Hudson, Moritz and Wearn[4] in a most enlightening study injected the coronary arteries at their ostia with solutions containing India ink, lamp-black or 10 per cent bismuth oxychloride under a positive pressure of 20 mm. of mercury for five minutes or longer with the heart *in situ*. The extracardiac coronary anastomoses shown in this manner were most extensive and widespread. From the major coronary vessels communications were shown to the pericardiophrenic branches of the internal mammary arteries and the anterior mediastinal, pericardial bronchial, superior and inferior phrenic, intercostal and esophageal branches of the aorta. The most extensive anastomoses between the cardiac and extracardiac vessels were around the ostia of the pulmonary veins but also along the root of the aorta, pulmonary artery, venae cavae and whereever the pericardial reflections occurred. As an extension of the same study Moritz, Hudson and Orgain[5] reported that in four patients the extracardiac coronary anastomoses were increased due to pericardial adhesions. Beck, Tichy and Moritz[6] employed this knowledge as a basis for the surgical production of pericardial adhesions to augment these extracardiac anastomoses.

Experimental Methods and Data

That there are significant extracardiac anastomoses with the coronary arterial bed is unquestioned. Whether these normal and slowly increasing (advancing age) intercommunications can be used as the pathway for rapidly increasing blood supply to the myocardium and promotion of intercoronary anastomoses remains to be proved. Undoubtedly such proof on a quantitative manner will be difficult if not impossible to obtain, for the very nature and diversity of the vascularity involved presents almost insurmountable problems for measurement. Great care must be taken in all experiments to avoid damage to the very vessels one is trying to evaluate.

To further verify the existence of a significant communication between the internal mammary and coronary arterial system injection studies were made in a series of normal dogs. Details of these experiments are in publication.[7] Their results were as follows:

1. Significant quantities of dye (Evans Blue, Fluorescein and I^{131}) injected into the internal mammary arteries at the level of the pericardiophrenic arteries were visualized in all animals in the small vessels throughout the parietal pericardium, in the mediastinal pleura and fat; around the base of the aorta and pulmonary artery and cavae; in the walls of the atria; in the epicardial fat over the atrioventricular grooves and repeatedly in the small plexus of vessels underlying the epicardium. In one in-

stance the entire thickness of the left ventricular myocardium was stained with dye even out into the base of the papillary muscles.

2. Gross dye mixed with blood was observed to flow from the distal ends of the transected circumflex or anterior descending artery in those dogs so prepared.

3. Radioactive iodine was found in the venous specimens removed from the coronary sinus in increasing amounts with the usual peak reached from five to 10 minutes after injection. The peak was somewhat variable but for the most part followed a set pattern.

4. One cm. segments of left ventricular myocardium and the posterior interventricular septum routinely contained radioactive iodine.

5. The source of this extracardiac arterial supply by the conditions of the experiment could only be by way of the pericardiophrenic artery to the parietal pericardium, thence to the myocardium under the epicardium along the roots of the great vessels and at the reflections of the pericardium.

As a natural corollary to these studies quantitative measurements of coronary backflow are desirable. As yet, these observations have not been made but preparations for such a study in this laboratory are in progress.

An attempt has been made to evaluate the degree of protection internal mammary artery ligation previously performed may afford the experimental animal when subjected to the production of sudden, acute myocardial infarction by ligation of the anterior descending coronary artery at its origin. The performance of this type of experimentation must likewise be done with great care and due regard to the variations in the anatomy of the left

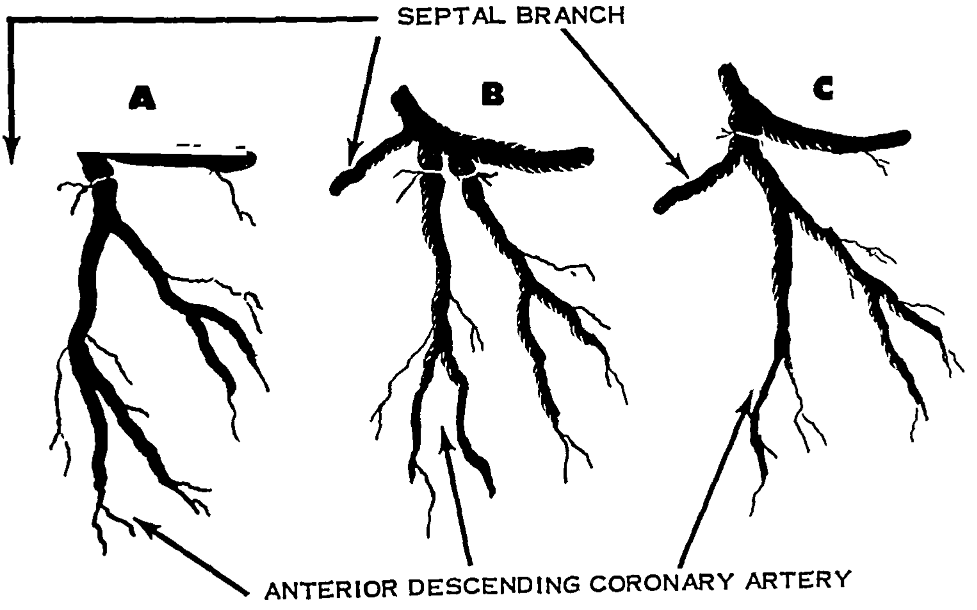


FIGURE 1: Diagram to show left coronary artery and its common variations. A is its usual pattern and point of ligation in these experiments. B—The first branch usually arising from the descending coronary shown arising from the circumflex coronary artery requiring a second ligature. C—Ligation at the origin of the descending coronary artery has inadvertently included a low lying septal branch (such ligations were excluded from this study).

coronary artery observed. The left coronary artery divides approximately 1 cm. from its origin at the aorta into the circumflex artery which continues around the heart in the atrioventricular groove and the anterior descending artery coursing down over the anterior aspect of the heart roughly overlying the interventricular septum. At this bifurcation but variably situated the septal branch arises and courses posteriorly in the interventricular septum. Just beyond the origin of the anterior descending artery its first branch which is rather large swings laterally and downward over the anterolateral aspect of the left ventricle. Thus ligation of the anterior descending artery in this experiment is designed to occlude both the anterior descending and its first branch as described but the septal branch is spared. Not infrequently the first branch of the anterior descending artery, instead of arising from its normal parent artery, arose from the first portion of the circumflex artery so that under these circumstances a separate ligature was employed to occlude it at this aberrant origin (Fig. 1). By following this method close uniformity was maintained throughout the experiment. It was hoped that survival in the control group would approximate 30 per cent so that infarct size could be compared with that of the "protected" group of animals. Dogs in the "protected" group were treated in the same manner but in these the internal mammary arteries were ligated immediately before, at 24 hours and at 48 hours before ligation of the anterior descending coronary.

In 14 control dogs the anterior descending coronary artery with the aforementioned branch to the anterolateral aspect of the left ventricle was ligated. Nine of these animals went into ventricular fibrillation and died within five to 20 minutes. Attempts to resuscitate them by defibrillation and massage were to no avail. Four others died within 24 hours. One dog lived two weeks and died in pulmonary edema. Thus, these control animals were judged on the basis of survival rather than upon size of infarction for obvious reasons.

SURVIVAL RATE IN DOGS FOLLOWING LIGATION OF DESCENDING CORONARY ARTERY

	Number of Dogs	Died at Operation	Died in 24 Hours	Survived 5 Days or More	Living
	14	9	4	1 (7%)	0
	UNPROTECTED				
5 min. to 45 min. before	4	0	1	3	2
24 hrs. before	7	1	2	4	2
48 hrs. before	8	3	1	4	3
TOTAL	19	4	4	11 (58%)	7 (36%)
PROTECTED BY BILATERAL LIGATION OF INTERNAL MAMMARY ARTERIES					

FIGURE 2: Total data obtained in 33 experiments to show a possible measure of protection provided to the myocardial circulation by bilateral internal mammary artery ligation (BIMAL).

In 19 dogs bilateral ligation of the internal mammary arteries was performed five to 45 minutes, 24 hours and 48 hours before ligation of the anterior descending coronary artery as above. The time interval seemed to make little or no difference in the degree of protection provided. Four

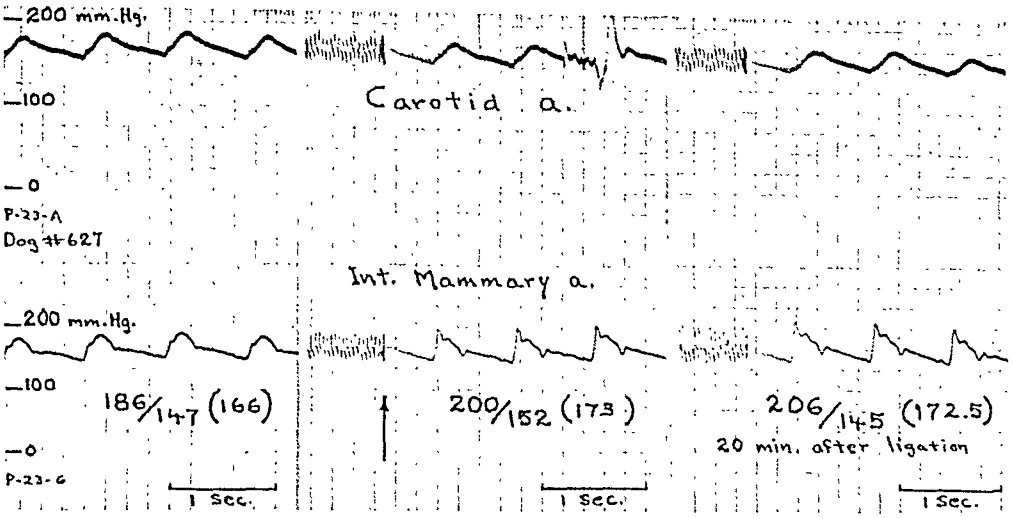


FIGURE 3: Direct pressure tracings taken within the internal mammary artery above the point of ligation at the second interspace. The arrow denotes the moment of ligation. A mean increase of 7 mm. Hg. above point of ligature is noted. The upper simultaneous tracing from the carotid artery shows the systemic pressure to remain constant.

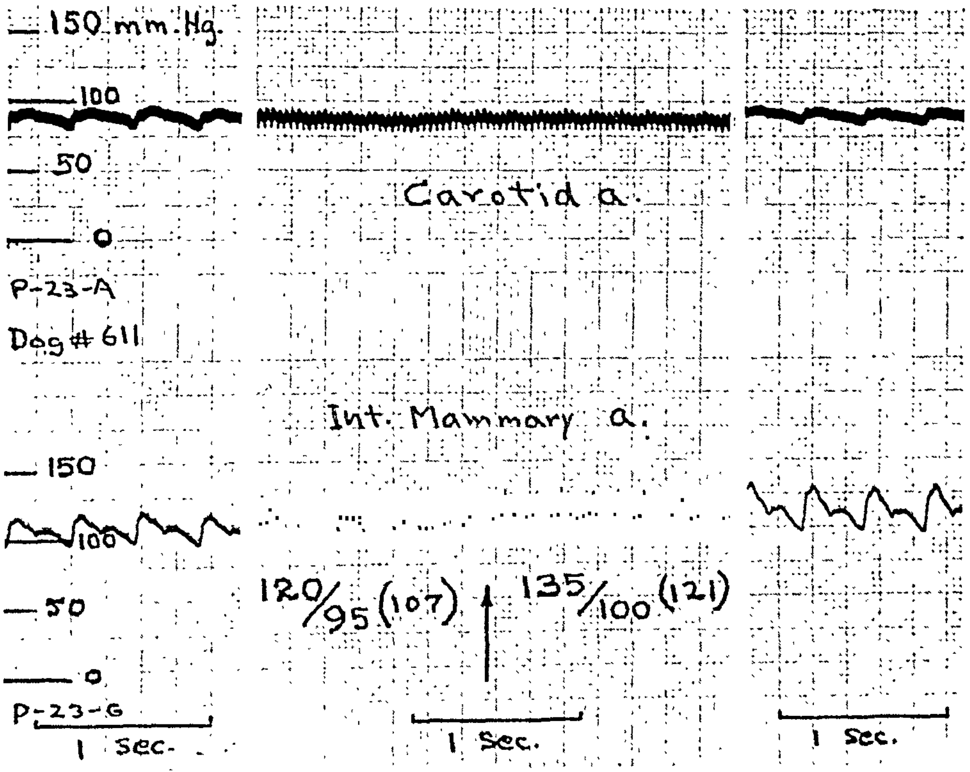


FIGURE 4: Direct pressure tracings taken within the internal mammary artery above the point of ligation at the second interspace. The arrow denoted the moment of ligation. A mean increase of 14 mm. Hg. above point of ligation is noted. Tracing on the right taken 30 minutes later.

of these animals died with a few minutes in ventricular fibrillation and four others died within 24 hours. The remaining 11 (58 per cent) dogs lived five or more days and seven (36 per cent) are still living having recovered completely (Fig. 2). Each heart of the 26 dogs who eventually died was carefully dissected and in each the septal branch from the left coronary artery was patent and uninjured. Six dogs in the original series, both among the protected and unprotected groups, were found to have had the septal branch inadvertently ligated with the anterior descending coronary artery, hence they were excluded from this analysis.

Under the conditions of this experiment which was closely controlled and meticulously performed it is felt that some degree of protection was obtained by bilateral mammary ligation in the manner described.

In an initial effort to investigate the hemodynamic pressure changes in the internal mammary artery above or proximal to the site of ligation,

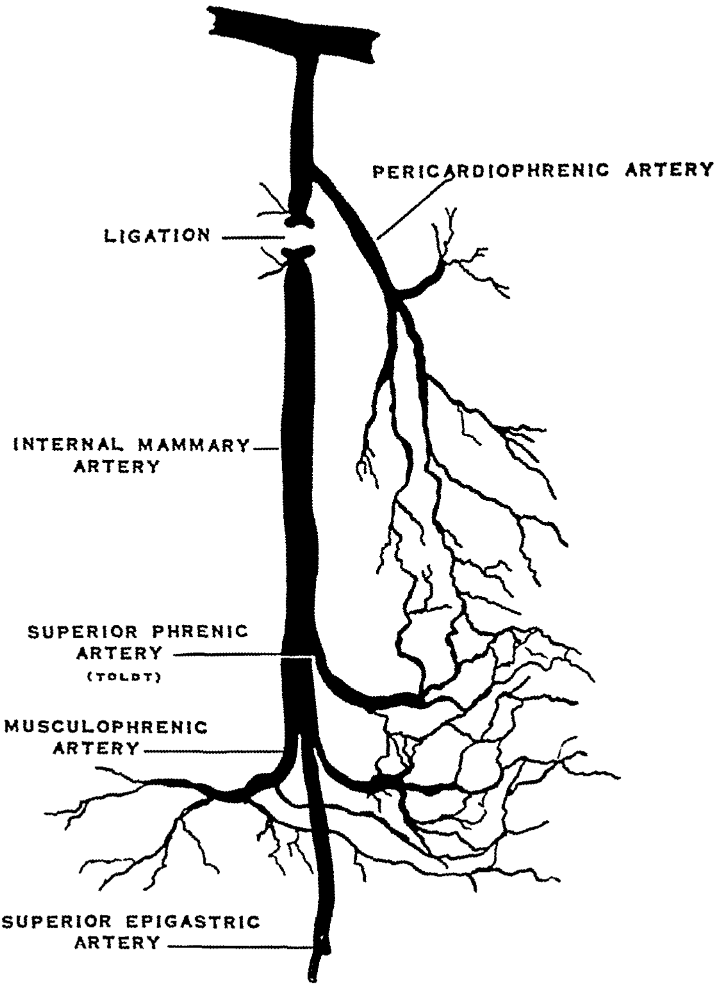


FIGURE 5: Schematic representation of internal mammary arterial collateral circulation as enhanced by ligation at the level of the second intercostal space.

pressure tracings were obtained in two animals. In one a mean pressure rise of 7 mm. Hg. (Fig. 3) was noted and in another a mean rise of 14 mm. Hg. (Fig. 4) was recorded. Each pressure rise was maintained for 20 to 30 minutes, the full period of observation. Simultaneous measurement of systemic arterial pressure in the left carotid artery showed no pressure variation.

Holman[8] has shown that "the collateral circulation which develops following ligation of a large artery depends upon transforming high "end pressure" in the parent artery into "lateral" pressure which, directed into its branches, results in an increased volume flow through them. This increased volume flow distends them and opens up their pre-arteriolar and arteriolar beds, whence the flow is directed into the pre-arteriolar beds of the branches distal to ligation, whose low pressure because of the ligation, permits blood to flow through them more readily then through pre-arteriolar beds elsewhere." This phenomenon would seem to occur in the case of the ligated internal mammary artery where the increased pressure proximal to the ligature is transmitted down the pericardiophrenic artery into the extensive arterial plexus over the parietal pericardium. These vessels freely anastomose with those from the superior phrenic, one of the two arterial terminations of the distal internal mammary artery completing the collateral circuit (Fig. 5). It is believed, and this specific point is presently under investigation in this laboratory, that this circuit is shared by the myocardium through its extracardiac communications with the pericardiophrenic arterial system and accounts for the clinical improvement in patients so treated. It must be clearly understood, however, that this supposition has not been proved and at present is pure speculation.

Clinical Application

Even as the experimental proof for the efficacy of a procedure of this type is difficult to obtain so also is the evaluation of its clinical application. It has long been recognized that the available clinical methods for objective measurement of the status and severity of coronary artery disease, acute or chronic, are woefully inadequate. Those who have pioneered so magnificently the direct surgical approach to the problem of coronary insufficiency (Beck,[9, 10] O'Shaughnessy,[11] Fauteux,[12] Thompson,[13] Vineberg[14] and others) have repeatedly commented upon the fact that the patient's own history and subjective information is of far more importance in ultimate evaluation than are the electrocardiogram or ballistocardiogram. This has been particularly true when surgical techniques involving pericardiotomy with trauma and the introduction of foreign bodies have been employed. It may be equally true of this technique even though the pericardium and pleura are not entered or disturbed.

Because all advocated techniques to date have required open thoracotomy, erroneously considered by most physicians as highly dangerous in itself, the proper use of myocardial revascularization by these means have never attained its measurable goal. They have rarely been given a chance on a wide scale or over a long period of time. This is perhaps the fault of the surgeon even more than of the physician because of the multiplicity of procedures advocated and their ever changing modifications. Possibly the introduction of internal mammary ligation as a means of myocardial revascularization because it is innocuous and easily tolerated even by the desperately crippled patient may break down the barrier of fear and open the way to a better understanding of what surgery has to offer. At this writing the authors are not laboring under the delusion that the operation herein reported is the *sine qua non* for coronary artery disease and should be used to the exclusion of all others. On the contrary the Beck I procedure and simple talc poudrage have demonstrated their value and are not to be abandoned or depreciated in the slightest without cause. Bilateral internal mammary artery ligation (BIMAL) to be considered on the same plane as current procedures has to prove its merit with the passage of time and time alone. It may well be that its proper place will be as an adjunct to existing measures. On the other hand should it eventuate in clinical results equal to those presently obtained by other means it will surely seek its own level and replace them. In any event it must be tested critically.

Brofman[15] has stated—"The one indication for operation is a positive diagnosis of coronary disease." A more succinct and definitive statement could not be made. The patients included in this series were just that. They fall into three categories:

1. Angina pectoris due to coronary insufficiency (arteriosclerosis or hypertensive) primarily post proved infarction, occasionally without proved antecedent infarction.

2. Arteriosclerotic heart disease with coronary insufficiency resulting in myocardial insufficiency—(a) episodic heart failure, (b) arrhythmias.

3. Hemodynamic coronary insufficiency (angina) due to aortic valvular disease. True coronary artery sclerotic changes may well be absent in this group.

With the inception of any new surgical procedure invariably the clinical material referred for its application represents the last stage of the disease in question—the case in which every other therapeutic measure has failed. The patients in this series were no exception to this time honored pattern.

Ninety-two patients have been operated upon to date, the first carried out on December 5, 1956. The criteria for surgery was the presence of organic coronary insufficiency with angina pectoris as outlined above. No patient with these findings was turned down because of age, debility, unstable disease, frequency and severity of attacks, hypertension, cardiomegaly, past cardiac failure or the like as has been the case in most series reported and treated by other surgical techniques. In other words they were not carefully culled so that only the better cases were selected. The youngest was 33 and the oldest 82 years of age. Twenty-five were over 60 years, of whom eight were over 70 and two over 80. Seventy-three were men; 19 were women.

Fifty of these patients have been carefully followed for from one to five months and form the basis of this initial analysis. Evaluation of the results obtained has been the sole responsibility of one cardiologist, Dr. J. Roderick Kitchell, Chief of Cardiology at Presbyterian Hospital. Thirty-four (68 per cent) have been clinically improved in that they either have no angina (18—36 per cent) or now have fewer and less severe attacks of pain (17—32 per cent). In most of these improvement or abolition of preoperative pain and discomfort was immediate, in some 48 to 72 hours were necessary and in a few, a week or ten days elapsed before the eventual result seemed complete. In 11 (22 per cent) no clinical improvement is now apparent although several seemed improved for a time. Five have died since surgery (Table I). Six of these patients were operated upon within two weeks of an acute infarction and three of these are now dead (see below). Seven more, making a total of 13, underwent surgery within six months of an acute infarction. Much could be added to this brief recitation of figures but in a disease so protean and unpredictable more time must pass before definitive statements should be made. Representative case histories of five of these patients exemplify the type of result obtained.

TABLE I

RESULTS OF BILATERAL LIGATION AND DIVISION OF THE INTERNAL MAMMARY ARTERIES

(50 Patients Followed 2 to 6 Months)

IMPROVED	TOTAL GROUP		44 Patients Under 70 Years	
	No.	Per Cent	No.	Per Cent
—Asymptomatic	18	35 or 68	18	32 or 73
—Moderate	11		11	
—Slight	5		3	
CLINICALLY UNCHANGED		11 or 22		9 or 20
Dead				
—Within one month	3	5 or 10		3 or 7
—Over one month	2			

Case 1: S. C., age 64 years, had hypertension discovered in 1937. Angina pectoris was first experienced in 1947 and one year later a posterior myocardial infarction occurred. Although her weight was gradually reduced from 173 lbs. to 126 lbs., she had angina of effort and right upper quadrant pain referrable to the gall bladder for the next seven years at which time cholecystectomy was performed. The angina persisted and in January 1956 left hemiparesis developed. In September 1956 she became bedfast with severe angina decubitus. She was unable to roll over or to laugh without producing severe angina. She had worn out the effect of nitroglycerin and peritrate and her pain was controlled only by the intramuscular injection of 400 to 600 mg. of demerol every 24 hours.

Physical examination revealed a well developed, elderly, white woman with a blood pressure of 140/90, pulse 84, and respirations 22. No cardiomegaly was present. There was a normal sinus rhythm and no murmurs were heard. A few moist rales in both lung bases could be heard. No masses or organs were palpable in the abdomen. There was no peripheral edema.

Routine laboratory examination revealed only a slight increase in the blood urea nitrogen to 20 mg. per cent. An electrocardiogram showed an old posterior infarction and marked anterior wall ischemia.

On January 25, 1957, she had bilateral ligation and division of the internal mammary arteries. During the next month she survived a moderately severe atypical pneumonia. Four months after operation she was still being maintained on digitalis and peritrate. Both she and her family physician recognized obvious improvement. She has been doing household chores, has taken short walks, and now negotiates the 28 steps to her second floor apartment. The clinical improvement in this patient has been almost unbelievable.

Present electrocardiographic tracings show considerable improvement in the ischemic pattern. No ballistocardiograms were taken in this instance.

Case 2: T. J., age 54, had been well until 1947 when he suffered a posterior myocardial infarction. He had returned to work but in 1949 severe substernal pressure radiating to the left arm and through to the back with emotional upsets, on exertion and later during sleep made its appearance. When this became progressive he changed to light work. Nitroglycerin relieved his pain but resulted in severe headaches. This drug recently was losing its effectiveness.

Physical examination revealed a well developed, somewhat obese, white man with blood pressure of 180/100, pulse 78, and respirations 16. The heart was not enlarged, there was a grade I systolic murmur at the apex, and normal sinus rhythm was present. The lungs were clear to auscultation and percussion. There was no palpable abdominal mass or organ. There was slight peripheral edema but no cyanosis.

Routine laboratory examination revealed only a modest increase in the serum cholesterol to 305 mg. per cent. The electrocardiogram showed an old posterior infarction and some anterior wall ischemia. Roentgen examination failed to reveal any cardiac chamber enlargement, but there was moderate dilatation of the aorta.

The internal mammary arteries were ligated and divided on February 22, 1957. Postoperatively, he was able to return to work. Three months after the operation he suffered a mild right sided stroke. At present he is engaged in light work, still has angina with exercise and after eating for which he takes brandy and Anacin. He is considered unchanged by this operation.

Electrocardiograms and ballistocardiograms since surgery show no evidence of improvement.

Case 3: J. D., age 57, had been in apparently good health aside from slight hypertension (176/100) and marked obesity until August of 1956 when he developed chills and fever up to 105° and became comatose. He was treated for pneumonia and after partial recovery his electrocardiogram showed the presence of a posterior myocardial infarction. Shortly thereafter rather severe left precordial pain on exertion developed. This could be relieved by nitroglycerin. There was no radiation of the pain. He resumed his work and while on a trip to Europe had a severe attack of indigestion requiring a narcotic. Despite diet, peritrate, and papaverine he continued to have anginal attacks on slight exertion.

On physical examination his blood pressure was 140/92 and his pulse was 76. He was an obese man (229 pounds) in no distress at rest. There were a few rhonchi and wheezes in the left lung base. There was no detectable cardiac enlargement. There was a soft, systolic murmur at the apex. The cardiac rhythm was normal sinus. Examination of the abdomen revealed an old cholecystectomy scar, and the liver was palpable just below the costal margin.

Routine laboratory examinations were normal. The electrocardiogram showed first degree A-V block and anterior wall ischemia. Roentgen examination revealed a dilated aorta but no cardiac enlargement.

Bilateral ligation and division of the internal mammary artery was accomplished on January 29, 1957, with an uneventful convalescence. Three months later he was again running his fuel oil business and very active without pain. He was considered markedly improved.

The electrocardiogram remained unchanged. Ballistocardiograms were not taken since surgery.

Case 4: J. S.: age 74, was in reasonably good health until four years prior to admission, when he began to experience exertional left precordial pain radiating to the left arm and jaw. These attacks progressed in severity and frequency and began to awaken him during the night. Two years prior to admission he suffered a cerebrovascular accident with left hemiparesis. His angina was relieved by rest and by nitroglycerin except for a more severe attack one week prior to admission which was accompanied by auricular fibrillation for which he was digitalized.

On physical examination his blood pressure ranged from 185/70 to 204/84, his pulse was 50. There was no cervical vein distension. The heart was not demonstrably enlarged and there was a grade II, systolic murmur heard at both the apex and base. The rhythm was normal sinus. The lungs were clear to percussion and auscultation. The liver was palpable 3 cm. below the costal margin on deep inspiration as was the spleen. There was no peripheral edema.

Routine laboratory examinations were essentially normal. The electrocardiogram suggested left ventricular hypertrophy with a brachycardia of 48. Roentgen examination of the chest revealed slight left ventricular enlargement. There was no significant aortic dilatation and the lungs were normal.

Bilateral ligation and division of the internal mammary artery was accomplished on February 28, 1957. Convalescence was uneventful.

Two and one-half months later he was still having some agina both in the daytime and during sleep. He was up and about the house and able to do a little light work. He was considered to be slightly improved if at all.

The electrocardiogram remained unchanged. Baliistocardiograms were not taken in this instance.

Case 5: A. G., age 41, had polycythemia vera as early as 1945. It was treated with radioactive P^{32} in 1950. He also had a history of gout. He experienced coronary thrombosis in 1951 followed by suffocating, constricting type of pain in the left chest brought on by the slightest exertion, excitement, or emotional upset. More recently this same pain awakened him from sleep on numerous occasions. He gained relief from nitroglycerin and was constantly on a maintenance dose of peritrate. In November, 1955 he had a second coronary thrombosis with resultant postero-septal infarction. Following this he was maintained on dicumarol for seven months until he developed retroperitoneal hemorrhage resulting in chills, fever, and hematuria that spontaneously resolved after the drug was discontinued. His angina progressed in frequency and severity and was accompanied by dyspnea on exertion.

On physical examination his blood pressure was 112/62, pulse 66, and respirations 22. There was no cervical venous distention. The heart was not enlarged. There was no murmur. The rhythm was normal sinus. The lungs were clear to percussion and auscultation. The abdomen was soft and the liver was palpable two finger breadths below the right costal margin on deep inspiration. There was no peripheral edema.

Routine laboratory examination revealed 16 gms. of hemoglobin. The red blood cell count was 6.1 million. The white blood cell count was 10.9 thousand. Urine analysis was normal. Serum cholesterol was 264 mg. The blood urea nitrogen was 17 mg. The blood uric acid was 12.4 gm. per cent. Roentgen examination of the chest revealed only a little prominence of the left ventricle and slight aortic dilatation. The electrocardiogram showed an old postero-septal infarct and present antero-apical ischemia.

On February 21, 1957, he underwent bilateral ligation and division of the internal mammary arteries. Convalescence was uneventful. He returned to the active management of his business without pain. He plays nine holes of golf but rides a motor scooter between holes, has danced and indulges in sexual intercourse for the first time in years without angina. This patient is markedly improved.

Some electrocardiographic improvement seems to be present in that the ST segments and T wave changes have returned toward normal. A postoperative ballistocardiogram taken during the first postoperative week showed no improvement and in fact did not appear to be as good as the preoperative tracings. This is almost routinely true in ballistocardiography after any operation be it abdominal or thoracic so that one must wait for at least one month after surgery before significance can be attached to such tracings.

The underlying pathologic basis for the coronary insufficiency in this group of patients has been summarized in Table II. Although the numbers of cases are far too few to permit conclusions to be drawn the very decided impression was gained that those with hypertensive cardiovascular disease obtained the better result. Whether the hypertension favored

TABLE II
RESULTS ACCORDING TO BASIC PATHOLOGIC PATTERN

	Arterio-sclerosis	Hypertension	Hemo-dynamic	
			Aortic Stenosis	Aortic Insufficiency
TOTAL	40	7	2	1
—Asymptomatic	12	3	2	1
—Moderate improvement	9	2	0	0
—Slight improvement	5	0	0	0
	26 (65) Per Cent	5 (71) Per Cent		
—Clinically unchanged	9	2	0	0
—Dead	5	0	0	0

the development of a higher gradient of pressure within the pericardiophrenic arterial collateral bed and therefore greater blood flow is conjectural at this point.

Of very considerable interest is the correlation of the clinical result obtained in these patients with the type and number of antecedent infarctions sustained. Such an analysis cannot be strictly accurate to the last detail for some overlapping is inevitable. The forty-five patients who have been clinically improved or unchanged suffered a total of forty-six infarctions, thus averaging approximately one infarction per patient. The five patients who died averaged more than two infarctions apiece and each of these patients suffered one septal infarction. The inference is that septal infarctions are the more hazardous and the least affected by this procedure (Table III).

Objective Findings

For some years after the introduction of true cardiac surgery there were many who could not accept the fact that patients were truly improved because of the great discrepancy between functional results and objective proof. No form of cardiac disease has shown itself to be more resistant to exact measurement than has coronary artery disease. This is not the fault of the pathologic entity but rather the inadequacy of professional instrumentation. The patient is certainly not to blame if he feels better, is more productive in society and is enjoying improved health to the consternation of the physician who just will not believe it because the improvement cannot be documented electrically. Wherein lies the answer?

Thirteen of these patients had electrocardiographic evidence of improvement and nine had improved ballistocardiograms. Curiously, only one showed improvement in both the ECG and the BCG. Thus, twenty-one patients (42 per cent) have shown objective improvement compared to 68 per cent showing clinical improvement. This comparison may not be entirely accurate for in only twenty patients have the ballistocardiograms been taken over a month from the time of surgery. Since the ballistocardiographic tracing most frequently deteriorates after any operative procedure during the first postoperative week and these patients were rou-

TABLE III
CORRELATION OF CLINICAL RESULTS WITH TYPE OF ANTECEDENT INFARCTION

	Anterior		Posterior		Septal		Ratio of Total Infarcts
	Old	Recent	Old	Recent	Old	Recent	Number of Patients This Group
Improved (34 Pts.)	9	3	13	0	11	1	37:34
Unchanged (11 Pts.)	2	2	2	0	2	1	9:11
Dead (5 Pts.)	3	0	3	0	3	2	11: 5

tinely discharged one week after surgery the ballistocardiographic data in over one-half of the patients (taken on the sixth postoperative day) may well be altered (Figs. 6 and 7).

Of the thirteen (26 per cent) who had *improved electrocardiographic* tracings after surgery the following changes were observed:

In ten the depressed ST segments returned toward normal (Figs. 6 and 7).

Nine had normal T waves.

Two had improvement in rhythm (Fig. 8).

One had a definite improvement in voltage.

In one the QRS was less slurred.

Paradoxically two patients who were unimproved clinically had improvement in their electrocardiograms and two patients who died of causes other than cardiac had brief improvement in their tracings.

Exercise tests of benefit were not employed in this series for the pre-

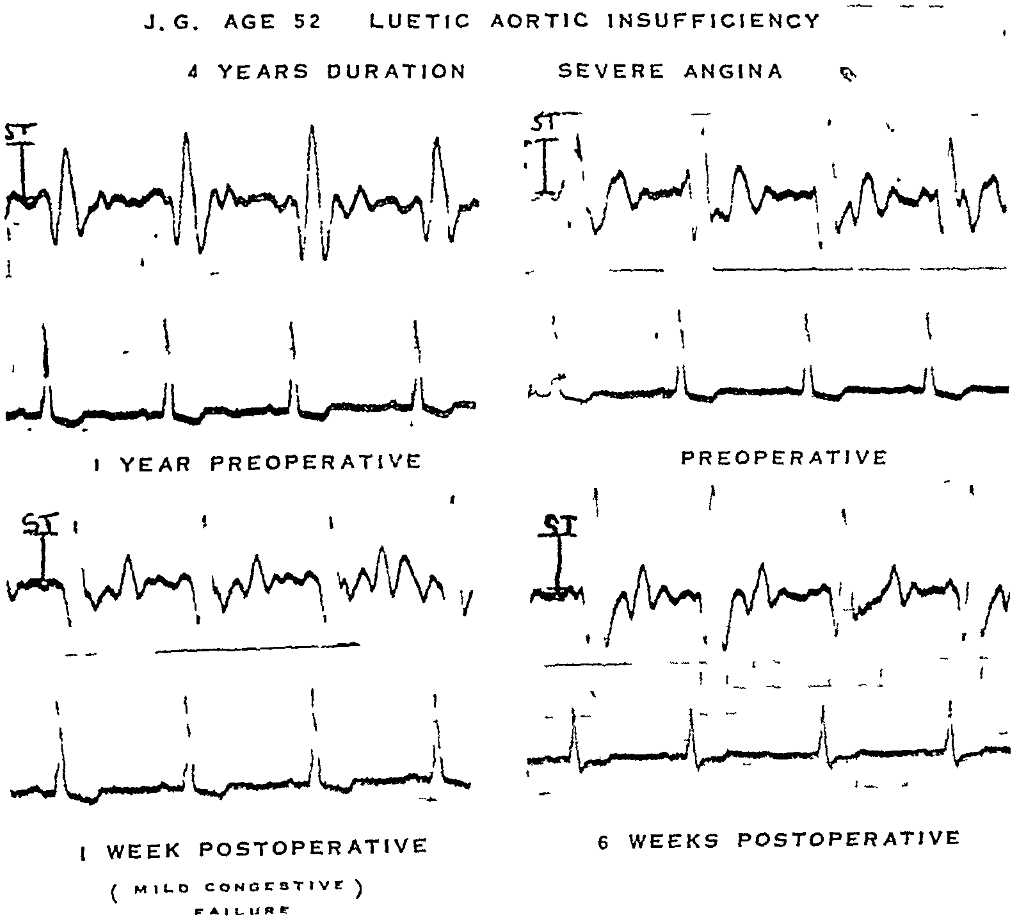

J. G. AGE 52 LUETIC AORTIC INSUFFICIENCY
4 YEARS DURATION SEVERE ANGINA
ST
ST
1 YEAR PREOPERATIVE
PREOPERATIVE
ST
ST
1 WEEK POSTOPERATIVE
(MILD CONGESTIVE FAILURE)
6 WEEKS POSTOPERATIVE

FIGURE 6: BCG and ECG tracings taken one year and two days before BIMAL (upper tracings) and one week and six weeks postoperative (lower tracing). Note the deterioration in BCG during the preoperative year, the fact that no essential improvement has occurred within the first postoperative week. In the six-week postoperative record note the considerably increased amplitude of the J waves *concomitant* with her marked clinical improvement.

operative diagnosis was not in question in any instance. It was felt unwise to risk the possible complication which occasionally follows such procedures in the more precarious stages of this disease.

Cause of Death

In only one of the five fatalities which occurred after surgery could there be any indictment of the surgery itself. This patient, a fifty-four year old white man, had suffered three posterior and one septal infarctions. For some hours prior to surgery anginal pain had been all but constant. The administration of Neosynephrin was necessary to obtain a blood pressure reading in the operating room. During the operation ventricular tachycardia was continuous (all cases are monitored by oscilloscopic and electrocardiographic recordings). In the recovery room his heart beat deteriorated and stopped and resuscitation was unsuccessful. The operation was obviously ill advised but there seemed to be nothing to lose and everything to gain by the attempt. An autopsy revealed several small infarctions, posterior and septal, but no large single area of necrosis. All coronary arteries showed advanced atherosclerosis. The right coronary artery was completely occluded one centimeter from its origin.

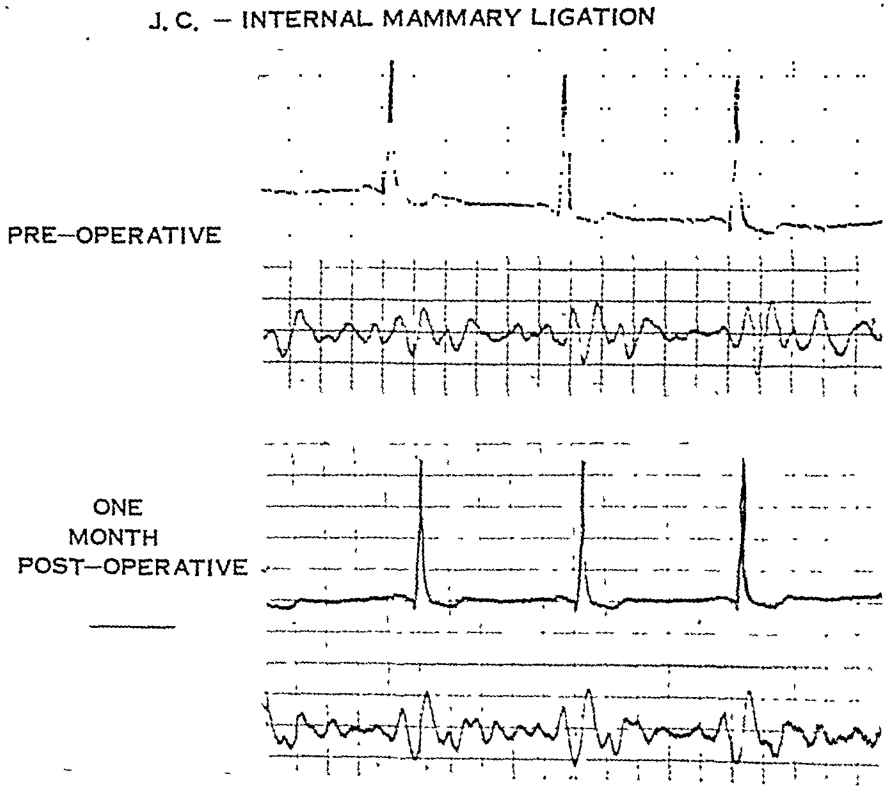


FIGURE 7: ECG and BCG tracings made preoperatively and one month postoperatively in a patient who obtained a marked improvement clinically. In the preoperative BCG record the abnormal H wave has nearly the same amplitude as the J wave. The postoperative record is practically normal with generalized improvement in amplitude.

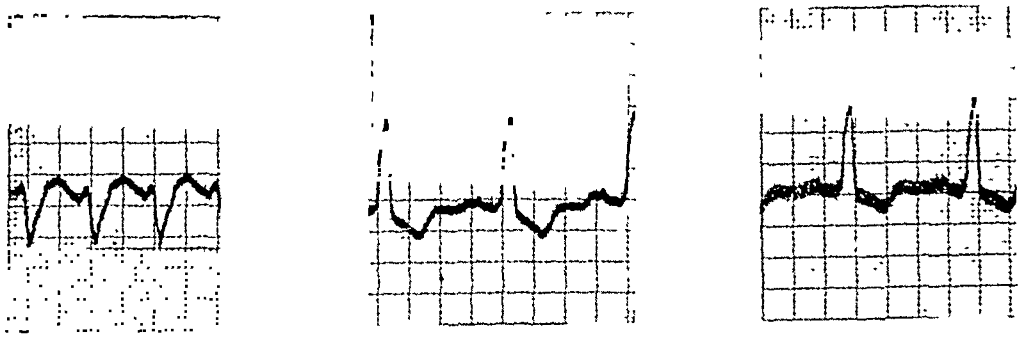
A second patient, white, male, age fifty-three, with two healed infarctions had suffered (noted in retrospect only as all the electrocardiograms had not been available) another septal extension eighteen days preoperatively. He was allowed out of bed on the day of surgery and increased his activities on the next two days. He collapsed and died suddenly on the third postoperative day. Had the recent infarction been suspected he would have been immobilized for several weeks.

The third patient, white, male, age sixty-five, with two previous infarctions, did exceptionally well clinically and was discharged on the sixth postoperative day. An ECG taken on the day of discharge was not read until the following week. He remained pain free and active despite an unappreciated small anterior subendocardial infarct which appeared on the final ECG. He died in his sleep on the ninth postoperative day.

Two other patients, elderly white females, aged seventy-two and eighty-two respectively, and suffering from a multiplicity of diseases in addition to old anterior and septal infarctions, died thirty-five and thirty-one days after mammary ligation from pyelonephritis, adrenal insufficiency and congestive heart failure with cardiomegaly in one and generalized lymphosarcoma in the other. Both obtained marked initial relief of angina and myocardial insufficiency until the terminal stages.

Surgical Technique

The performance of bilateral division of the internal mammary arteries as compared to other surgical procedures for cardiac disease is safe, simple and innocuous in capable hands. Although the technical risk is negligible one must remember that the disease being treated is highly lethal.



3/4/57
LEAD I (PRE—OP)
VENTRICULAR
TACHYCARDIA

3/5/57
LEAD I (PRE—OP)
NORMAL SINUS
RHYTHM

3/12/57
LEAD I (POST—OP)

FIGURE 8: ECG tracing in a patient subject to frequent attacks of ventricular tachycardia requiring intravenous pronestyl. There has been only one mild attack postoperatively. *Note the shift in axis in lead I in transition from ventricular tachycardia to the patient's usual left bundle branch block.*

The application of this procedure and any other will inevitably be followed by the morbidity and mortality of severe coronary artery disease for such operations are palliative not curative.

The choice and conduct of anesthesia is of paramount importance. Two types have been used. For those whose condition is precarious and unstable a local anesthetic, 0.5 per cent procaine, is used. One side is injected and operated completely and then the other. This avoids the sudden introduction of too much anesthetic which may tend to lower the blood pressure. No more than 50 cc. of solution is necessary when used properly. Those patients who are in good condition and in whom the disease is reasonably stable easily tolerate a light general anesthesia of sodium pentothal induction and maintenance on 50 per cent N_2O and O_2. Small amounts of succinyl choline may be used as a supplement. Endotracheal intubation is not necessary but should be available.

Bilateral hockey stick incisions are made at the lateral borders of the sternum in the second interspace. Simple transverse incisions are adequate but provide very limited exposure when the interspace is narrow and the musculature well developed. The curved incision with its reflected flap exposes the entire interspace without restriction. The pectoralis muscle is split and retracted in a normal line of cleavage. The intercostal muscles are incised midway and parallel to the ribs. The fat overlying the pleura is encountered as it surrounds the mammary vessels commonly lying one finger's breath lateral to the sternal margin. The vein courses immediately medial to the artery and is left intact. Great care and patience must be exercised when mobilizing the artery from its areolar attachments to the pleura. The artery is divided between ligatures. The right internal mammary artery is commonly larger than the left.

The procedure may be considerably more difficult than it sounds in heavy-set, thick-muscled males. Hemorrhage and inadvertent opening of the pleura can be the only complications and usually are readily controlled. Significant changes in blood pressure must be avoided. Oscillographic and electrocardiographic monitoring is desirable but not essential.

SUMMARY AND CONCLUSIONS

1. A critical although purely preliminary attempt has been made to assess the value of bilateral ligation and division of the internal mammary arteries as a means of increasing blood supply to the myocardium. The concept for this approach is that of Fieschi. Battezzati, Tagliaferro and DeMarchi have been responsible for reintroducing and amplifying this original concept. By and large the studies reported in this discussion confirm the findings of these Italian investigators. At the moment, however, considerable reservation as to the ultimate place of this surgical procedure is warranted. Whether it will eventually remain as a surgical entity on its own merits or will be used as an adjunct to other surgical techniques cannot be decided until much more investigative work, both experimental and clinical, has been carried out.

2. That there is a naturally developing extracardiac communication between the coronary arterial and pericardiophrenic arterial vasculature has again been confirmed.

3. As yet there is no experimental proof that ligation of the internal mammary arteries bilaterally at the level of the second interspace actually increases blood flow to the heart although the supposition that it does is entertained.

4. There is the decided suggestion that in dogs ligation of the internal mammary arteries provides a measure of myocardial protection to the subsequent production of acute coronary occlusion by ligation of the anterior descending coronary artery at its origin.

5. Ligation of the internal mammary arteries at the second interspace is followed by an increase in mean arterial end pressure above the point of ligature in dogs.

6. Ninety-two patients suffering from arteriosclerotic and hypertensive cardiovascular disease with organic coronary insufficiency and angina pectoris have been subjected to bilateral mammary artery ligation (BIMAL). The angina pectoris in three of these patients was secondary to advanced aortic valve disease. Fifty of these patients have been carefully followed for one to five months. By conservative clinical evaluation 34 (68 per cent) of these patients have either lost their symptoms of pain (18—36 per cent) or have been immeasurably relieved of their discomfort (17—32 per cent). The remainder were unimproved.

7. Objective evidence of clinical improvement lags well behind the observed clinical improvement. In 13 (26 per cent) the electrocardiographic tracings taken one month or more after surgery show obvious improvement and the same may be said in nine (18 per cent) of the ballistocardiographic studies obtained. As this evidence of improvement occurred on only one occasion in the same patient, objective signs for the better have occurred in 22 (42 per cent) patients. We are indebted to and acknowledge the very considerable help rendered by Dr. Isaac Starr, Hartzell Research Professor of Therapeutics, University of Pennsylvania Medical School, who supervised and read all ballistocardiograms.

8. A simple technique for the performance of Division of the Internal Mammary Arteries has been detailed.

Addendum

A total of 150 patients suffering from organic coronary insufficiency have now been treated by bilateral ligation and division of the internal mammary arteries by the authors. Results to date in this larger series closely follow those herein reported.

RESUMEN

1. Se ha hecho intento crítico aunque netamente preliminar para estimar el valor de la ligadura bilateral de las arterias mamarias internas como un recurso para aumentar el flujo sanguíneo hacia el miocardio.

2. Las investigaciones iniciales de laboratorio confirman el desarrollo de una comunicación natural entre el sistema arterial pericardiofrénico y las raíces periféricas del sistema de la arteria coronaria.

3. En los perros, la ligadura de las mamarias internas parece haber proporcionado cierta protección del miocardio cuando más tarde se hizo a ligadura de la arteria coronaria anterior ascendente. Todavía no hay prueba experimental medible de que la ligadura de las mamarias internas haya resultado en aumento del flujo sanguíneo miocárdico.

4. Se han sujetado a la ligadura bilateral de las mamarias (BIMAL) noventa y dos enfermos de enfermedad arterioesclerosa y cardiovascuar hipertensiva con insuficiencia orgánica coronaria y angina de pecho.

En tres de estos enfermos la angina de pecho era secundaria a una enfermedad valvular avanzada de la aorta. Cincuenta de estos enfermos se han observado cuidadosamente de uno a cinco meses. Después de una valuación conservadora, 34 (68 por ciento) han perdido sus síntomas dolorosos; 18 enfermos (o sea el 36 por ciento) o bien se han aliviado de sus molestias inmensamete (17 enfermos o sea el 32 por ciento). El resto no mejoraron.

5. La evidencia objetiva de la mejoría clínica es mucho menor que la mejoría clínica observada. En 13 (25 por ciento) los trazos electrocardiográficos tomados un mes o más después de la operación muestran clara mejoría y lo mismo es de decirse en 9 (18 por ciento) de los estudios balistocardiográficos obtenidos. Como esta evidencia de mejoría ocurrió sólo una vez en el mismo enfermo, los signos objetivos de mejoría ocurrieron en 22 (42 por ciento).

RESUME

1. Une étude critique mais encore tout à fait préliminaire, a été faite pour juger de la valeur de la ligature bilatérale et de la division des artères mammaires internes, pour augmenter l'apport sanguin au myocarde.

2. Les premières investigations de laboratoire confirment qu'une communication se développe naturellement entre le système artériel péricardiophrénique et les ramifications périphériques du système artériel coronarien.

3. Chez les chiens, la ligature des artères mammaires internes semble avoir fourni un moyen de protection myocardique lorsque la ligature de l'artère coronaire antérieure descendante était pratiqués ultérieurement. Jusqu'à présent, il n'y a aucune preuve expérimentale que la ligature des artères mammaires internes ait produit une augmentation du volume sanguin myocardique évaluable.

4. 92 malades souffrant d'affections cardio-vasculaires athéromateuses et hypertensives avec insuffisance coronarienne organique et angine de poitrine ont été soumis à la ligature bilatérale de l'artère mammaire interne. Chez trois de ces malades, l'angine de poitrine était secondaire à une affection grave de la valvule aortique. 50 de ces malades ont été suivis soigneusement pendant un à cinq mois. Des études cliniques suivies

ont montré que 34 de ces malades (68%) ou bien ont vu disparaitre leurs symptômes douloureux (18 malades ou 36%) ou bien ont été incontestablement soulagés de leur gêne (17 malades, 32%). Le reste fut sans amélioration.

5. La preuve objective de l'amélioration laisse loin derrière elle l'amélioration constatée par simple observation clinique. Chez 13 malades (25%) les tracés électrocardiographiques pris un mois ou plus après l'intervention montrent une amélioration évidente et on peut en dire autant de 9 malades (18%) sur les études ballistocardiographiques qui ont été obtenues. Comme cette preuve amélioration n'a été constatée qu'une fois chez chaque malade, les signes objectifs d'amélioration peuvent être portés au nombre de 22 (42%).

ZUSAMMENFASSUNG

1. Es wurde ein kritischer, gleichwohl durchaus vorläufiger Versuch unternommen zwecks Bemessung des Wertes der bilateralen Ligatur und Durchtrennung der art. mam. int. als einem Verfahren zur Steigerung der Blutzufuhr des Myocards.

2. Initiale Laboratoriumsuntersuchungen bestëtigen das Bestehen einer sich natürlich entwickelnden Verbindung zwischen dem Herzbeutel-und dem Zwerchfell-Arteriensystem und den peripheren Ursprüngen des Coronararteriensystems.

3. Bei Hunden scheint die Ligatur der art. mam. int. eine Massnahme zum Schutze des Myocards geschaffen zu haben, wenn anschliessend eine Ligatur der vorderen absteigenden Coronararterie vorgenommen wurde. Bisher liegt noch kein messbarer experimenteller Bewies dafür vor, dass die Ligatur der art. mam. int. eine vermehrte Durchströmung des Myocards zur Folge hat.

4. 92 Kranke, die an arterio-sklerotischen und hypertonischen cardiovasculären Krankheiten mit organischer Coronar-Insuffizienz und Angina pectoris litten, wurden einer bilateralen Ligatur der art. mam. int. unterzogen (BIMAL). Die Angina pectoris bei 3 dieser Kranken war die Folge einer beträchtlichen Erkrankung der Aortenklappen. 5 dieser Kranken wurden 1-5 Monate lang sorgfältig weiter beobachtet. Nach vorsichtiger *klinischer Bewertung* haben 34 (68%) dieser Kranken entweder die Schmerzerscheinungen verloren (18 Pat. oder 36%) oder wurden in nicht messbarem Grade von ihrem Unbehagen befreit (17 Pat. oder 32%). Die übrigen blieben ungebessert.

5. Die objektiven Anhaltspunkte für die klinische Besserung blieben deutlich hinter der beobachteten klinischen Besserung zurück. Bei 13 Kranken (25%) ergaben die elektrocardiographischen Aufzeichnungen, die 1 Monat oder später nach der Operation erfolgt waren, eine unverkennbare Besserung, und das gleiche kann von 9 (18%) der angestellten ballistocardiographischen Untersuchung gesagt werden. Da dieses Zeichen der Besserung nur ein einziges Mal bei dem gleichen Kranken vorkam, traten objektive Zeichen zum Besseren bei 22 Kranken auf (42%).

REFERENCES

1 Battezzati, M., Tagliaferro, A. and De Marchi, G.: "The Ligature of Two Internal Mammary Arteries in Disorders of Vascularization of the Myocardium," *Minerva Medica*, 46: (Part Two) 1173, 1955.

2 Langer, L.: "Die Foramina Thesesii im Herzen des Menschen, Sitzungsberichte Akad. Wissensch.," *Math.-naturwissensch. Cl., Wien*, 82:25, 1880.

3 Gross, L.: *The Blood Supply to the Heart*, New York, Hoeber, 1921.

4 Hudson, C., Moritz, A. and Wearn, J.: "The Extracardiac Anastomoses of the Coronary Arteries," *J. Exper. Med.*, 56:919, 1932.

5 Moritz, A., Hudson, C. and Orgain, E.: "Augmentation of the Extracardiac Anastomoses of the Coronary Arteries Through Pericardial Adhesions," *J. Exper. Med.*, 56:927, 1932.

6 Beck, C. S., Tichy, V. L. and Moritz, A. R.: "Production of Collateral Circulation to the Heart," *Proceedings of the Soc. Exper. Biol. and Med.*, 32:759, 1935.

7 Glover, R. P. and Davila, J. C. with Kyle, R. H., Beard, Jr., John C., Trout, R. G., and Kitchell, J. R.: "Ligation of the Internal Mammary Arteries as a Means of Increasing Blood Supply to the Myocardium," *J. Thoracic Surg.* In press.

8 Holman, E.: "Problems in the Dynamics of Blood Flow: 1. Conditions Controlling Collateral Circulation in the Presence of an Arteriovenous Fistula, Following the Ligation of an Artery," *Surgery*, 26:889, 1949.

9 Beck, C. S.: "Development of a New Blood Supply to the Heart by Operation," *Ann. Surg.*, 102:801, 1935.

10 Beck, C. S.: "Revascularization of the Heart," *Ann. Surg.*, 128:854, 1948.

11 O'Shaughnessy, L.: "Surgical Treatment of Cardiac Ischemia," *Lancet*, 1:185, 1937.

12 Fauteux, M.: "Pericoronary Neurectomy Associated with Ligature of Great Coronary Vein in Treatment of Some Forms of Coronary Disease," *Union Medicale du Canada*, 74:424, 1945.

13 Thompson, S. A. and Raisbeck, M. J.: "Cardio-cardiopexy: The Surgical Treatment of Coronary Arterial Disease by the Establishment of Adhesive Pericarditis," *Ann. Int. Med.*, 16:495, 1942.

14 Vineberg, A. M.: "Development of Anastomoses Between Coronary Vessels and Transplanted Internal Mammary Artery," *J.A.M.A.*, 55:117, 1946.

15 Brofman, B. L.: "Surgical Treatment of Coronary Artery Disease: Medical Management and Evaluation of Results," *Dis. Chest*, 31:253, 1957.

Cor Pulmonale:
A Semantic Consideration, with Brief Notes on Diagnosis and Treatment

I. C. BRILL, M.D.
Portland, Oregon

There is a conspicuous lack of agreement as to what lesions or clinical conditions should be included in the term "cor pulmonale." Varied and conflicting views prevail throughout the literature, current and old.[1-18]

Historically, the first use of the term cor pulmonale appears to have been in 1931 by Paul White;[1] prior to this time "emphysema heart" was in common use. In the first edition of his textbook on heart disease White speaks of "pulmonary heart disease or cor pulmonale" and indicates prefference for the latter term. Twenty years later (4th edition)[2] he continues to speak of "cor pulmonale or pulmonary heart disease," using these terms as synonyms. In discussing the etiology of cor pulmonale he stresses "chronically increased resistance in the pulmonary circulation due commonly to narrowing of the arterioles and capillary bed," but specifically excludes from this category resistance due to "left heart failure, mitral stenosis, or congenital heart disease."

In a recent review Fishman and Richards[3] define cor pulmonale as "a heart which manifests dilatation, hypertrophy, or failure secondary to intrinsic disease of the lungs;" they specifically exclude from this definition "right ventricular hypertrophy, dilatation or failure secondary to disease of the heart, e.g. mitral stenosis." On the other hand, Griffith[4] includes right ventricular changes of mitral stenosis in the general category of cor pulmonale; he makes a distinction between "primary" cor pulmonale in which "pulmonary hypertension is the basic lesion" and "secondary" cor pulmonale "in which the basic lesion lies not in the pulmonary circuit but beyond, in the left side of the heart."

Oram[5] broadily defines cor pulmonale as "hypertrophy and eventual failure of the right ventricle resulting from disease of the lungs, or *disorder of the pulmonary circulation.*" However, when he lists the specific lesions causing disorders of the pulmonary circulation he omits all congenital cardiac lesions. Mack and Snider[6] define cor pulmonale as "right ventricular hypertrophy resulting from disease involving the lung and pulmonary circulation" but exclude from this category "other causes of right ventricular hypertrophy, such as mitral stenosis, congenital heart disease, and left ventricular failure." Hecht,[7] however, includes pulmonary valvular stenosis as well as "pure mitral stenosis" in which "secondary vascular changes (in the pulmonary bed) develop, apparently the result of long-standing pulmonary vascular congestion, high capillary and arte-

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From the Department of Medicine, University of Oregon Medical School.

*For a comprehensive discussion of this phase of therapy and a detailed description of specific measures the reader is referred to a recent article by Simon Dack.[18]

riolar pressure and precapillary and interalveolar edema." The latter author also feels that "For the sake of completeness elevation or right-sided pressure as the usual consequence of left ventricular failure should be mentioned."

Some authors[3, 9] restrict the use of the term cor pulmonale to right ventricular lesions resulting from disease of the lung only. While it is true that intrinsic lung disease is a common cause of right ventricular strain and failure, clinical and anatomical studies indicate that the development of cor pulmonale in such cases is dependent on associated involvement of the pulmonary vascular bed. Parenchymal lung disease per se, however extensive, may leave the right ventricle completely intact if there is no coincidental interference with the flow of blood through the pulmonary circuit. Some years ago when performing postmortem examinations in a tuberculosis hospital it was impressive to observe the frequency with which a normal right ventricle is seen in the presence of extensive diffuse pulmonary parenchymal disease. Later experience in clinicopathological conferences has confirmed this earlier impression (Figure 1).

Similar observations are frequently found in the literature. Spatt and Grayzel[8] state "The mechanism of dilatation and hypertrophy of the right

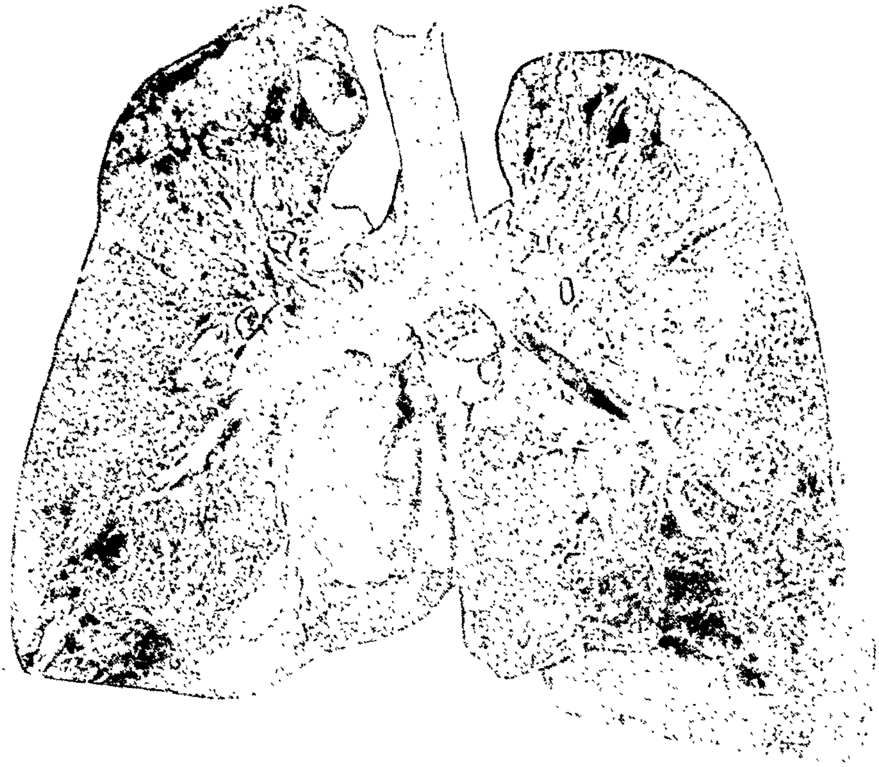

FIGURE 1: Photograph of the cut surfaces of both lungs of a patient who died of pulmonary tuberculosis; there was extreme, diffuse parenchymal disease. The heart was entirely normal. (Autopsy by Dr. Nelson Niles of the Department of Pathology of the University of Oregon Medical School.)

ventricle (in diffuse pulmonary disease) seems fairly generally agreed upon. The pulmonary changes destroy and narrow blood capillaries in the lungs, causing pulmonary hypertension, which in turn increases the strain on the right heart, thus resulting in dilatation and hypertrophy." Rubin[9] states that in the absence of associated cardiovascular disease, a selective or preponderant enlargement of the right ventricle in emphysema is an uncommon finding. Florence McKeown[10] in a postmortem study of 101 cases of emphysema found hypertrophied right ventricles in 39 and normal right ventricles in 62 cases. White and Brenner[11] in a study of 100 consecutive unselected autopsies found that "the majority of cases with pulmonary disease had normal right ventricles. . . . . .There was relative little correlation between changes in the pulmonary vascular tree and thickness of the right ventricles *except in the more marked cases*. . . . . Ordinarily, asthma, emphysema and pulmonary tuberculosis, even though of high degree, do not produce cor pulmonale."

It is thus apparent that parenchymal lung disease alone does not necessarily produce strain or hypertrophy of the right ventricle. On the other hand, it is a common experience to find right ventricular hypertrophy whenever the pulmonary circulation is disturbed, even in the total absence of parenchymal lung disease. As examples of such pathological states one may cite primary pulmonary vascular sclerosis, essential pulmonary hypertension, and obstruction of the main stem of the pulmonary artery by tumor, aortic aneurysm or valvular stenosis. Hence, it would appear fair to state that in all instances where isolated right ventricular hypertrophy develops, the crucial lesion is a disturbed pulmonary circulation.

A disturbed pulmonary circulation may result from various pathological processes:

A. "Organic" Pulmonary Vascular Disease. Arteriosclerotic and/or thrombo-embolic narrowing of the pulmonary arteries and their branches (with secondary pulmonary hypertension) may be either primary as in primary pulmonary vascular sclerosis or secondary to some other pathological process. Examples of the latter are: (1) pulmonary parenchymal disease, (2) congenital cardiovascular disease, such as patent ductus arteriosus, septal defects, and other lesions with abnormal communication between the systemic and pulmonary circulation, (3) acquired cardiovascular lesions such as mitral stenosis and left ventricular failure, (4) peripheral vascular disease such as phlebothrombosis of the legs and pelvis, (5) blood dyscrasias such as polycythemia, primary or secondary, sickle-cell anemia, leukemia.

B. Hypoxia and Hypercapnia. Hypoxemia and hypercapnia due to impaired pulmonary ventilation, such as may be seen in chronic bronchitis and emphysema, may produce pulmonary hypertension with or without demonstrable morphologic changes in the pulmonary vessels. The right ventricular hypertrophy which often occurs in such cases may be due to the hypertension alone or to the combined effect of the hypertension and the hypoxemia.

C. Essential Pulmonary Hypertension. Cases of pulmonary hypertension proved by cardiac catheterization, have been observed in which no cause for the hypertension could be demonstrated either clinically or at autopsy. It may be assumed that in such cases the hypertension and the right ventricular hypertrophy resulted from arteriolar spasm of sufficient degree to interfere with the flow of blood through the lesser circulation.

D. Hypervolemia. Strain of the right ventricle may occur even in the absence of diffuse organic pulmonary vascular disease when the volume of blood propelled through the pulmonary circuit is increased. Such a condition obtains in the presence of septal defects and other congenital lesions with abnormal communications between the lesser and systemic circulations, in pulmonary arterio-venous aneurysms, and in polycythemia, primary or secondary.

E. Mechanical Obstruction. Obstruction to the right ventricular outflow tract may result from valvular lesions—especially pulmonic stenosis, coarctation of the pulmonary artery and compression of that vessel by tumor or aortic aneurysm.

F. Chest Deformities. Kyphoscoliosis and pectus excavatum are important examples. The exact mechanism by which these lesions cause strain on the right side of the heart is not completely established. Available evidence implicates pulmonary infection and emphysema secondary to compression of portions of the lung.[12]

Right ventricular response to disordered pulmonary circulation, regardless of etiology, is constant. If a hypertrophied right ventricle were isolated from the rest of the heart, the most discerning pathologist would be unable to tell whether the cause of the hypertrophy lay in diffuse lung disease, a congenital cardiac lesion, or pulmonary hypertension due to any of the anatomical or physiological abnormalities described above.

Within this broad range, the electrocardiogram also is non-specific, revealing an "RVH" (cor pulmonale) pattern but not its cause (Figure 2). To a more limited extent this is also true of x-ray film silhouettes, especially if only posteroanterior films are available (Figure 3).

Thus three facts stand out: (1) pulmonary parenchymal disease alone, if it fails to disturb the pulmonary circulation, does not produce right ventricular hypertrophy; (2) any condition which brings about increased resistance to the flow of blood through the pulmonary vascular bed may cause right ventricular strain, hypertrophy and eventual failure; (3) the clinical and pathological manifestation of such right ventricular hypertrophy and failure follow a fixed pattern—modified only by the symptoms obviously due to the associated disease—regardless of the condition which has disturbed the pulmonary circulation.

In the light of these considerations it would seem reasonable to regard "cor pulmonale" as a generic term comprising all types of right ventricular strain and hypertrophy due to a disordered pulmonary circulation regardless of etiology. In this sense it is analogous to "cor aortale" which refers to strain and hypertrophy of the left ventricle due to a disordered systemic (aortic) circuit, as in systemic hypertension, coarctation of the aorta and aortic valvular disease. The difficulty in arriving at a concise

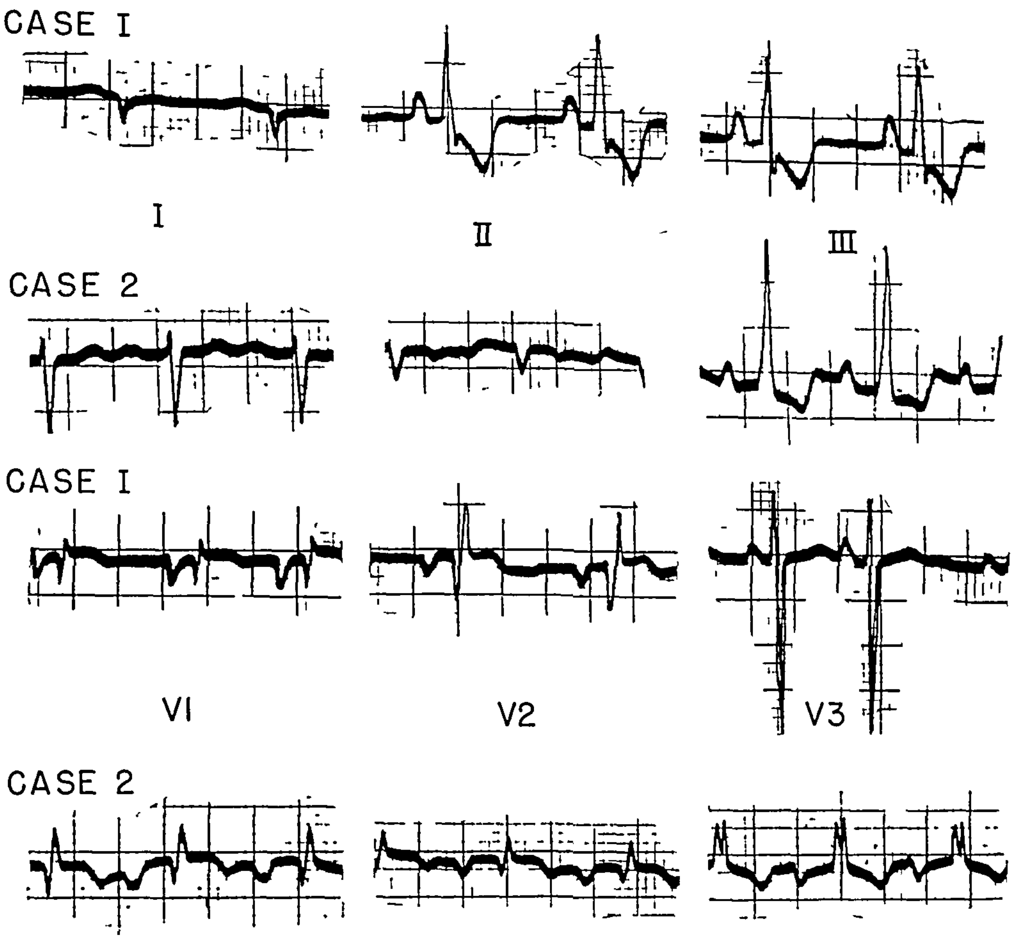

FIGURE 2: The electrocardiographic tracings on these two patients show striking similarity in the demonstration of right ventricular hypertrophy. In *Case 1,* the patient, a 56 year old woman, was found at autopsy to have intimal pulmonary arteriolar sclerosis; while in *Case 2,* a 36 year old woman, the cause for right ventricular hypertrophy was an interatrial septal defect.

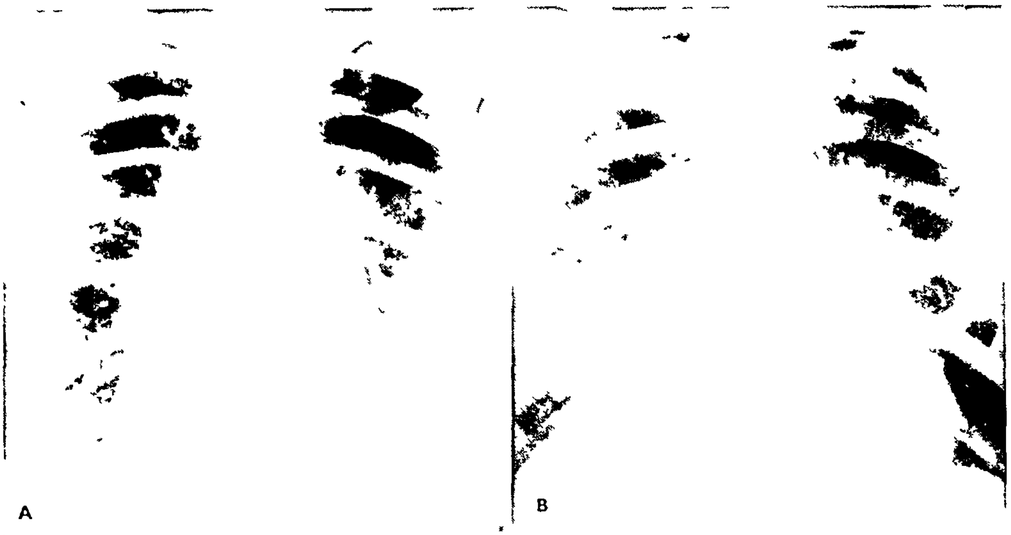

FIGURE 3A FIGURE 3B

FIGURE 3: Right ventricular hypertrophy due to: A, primary pulmonary vascular sclerosis in a 37 year old woman (autopsy), and B, mitral stenosis in a 37 year old man (surgery).

definition of cor pulmonale lies in the fact that the type of heart disease covered by that term may occur in a large variety of unrelated clinical and pathological conditions. However, when it is made clear that all these "unrelated" conditions have one thing in common, a disturbed pulmonary circulation, the difficulty disappears, and cor pulmonale may then be defined simply as right ventricular hypertrophy, strain or failure due to disordered pulmonary circulation. "Pulmonary heart disease," "emphysema heart" and "pulmonary hypertensive heart disease," often used as synonyms of cor pulmonale are less generic in their connotation. Each of these terms refers to a more or less specific etiology of the right ventricular lesion; whereas "cor pulmonale" includes all these as well as other varieties of isolated right ventricular hypertrophy due either to pulmonary or extra-pulmonary factors.

Diagnosis

This concept of cor pumonale focuses attention upon the essential pathologic physiology. In any given case consideration of the various pathological processes which may disturb the lesser circuit points the way to a more definitive etiological diagnosis.

A history of chronic pulmonary disease is present in most instances. In cases secondary to mitral stenosis there is a background of rheumatic carditis dating from childhood. In primary pulmonary vascular disease or in primary pulmonary hypertension the history of illness is of relatively short duration—a few months to a year or two. The early manifestations are those of the underlying disease upon which are superimposed, gradually or abruptly, the symptoms of pulmonary hypertension. The latter include fatigue, dyspnea, cyanosis (often paroxysmal), dizziness, syncope and angina-like chest pains with atypical radiation. Once the symptoms become pronounced the course is rapidly downhill, terminating fatally within weeks or months. Sudden death is common.

Pertinent physical signs are dyspnea, apprehensiveness and cyanosis. Clubbing of the fingers may be present. The heart may or may not show enlargement to percussion. However, palpation will reveal a pronounced lower sternal thrust and increased systolic pulsations in the area of the conus arteriosus. A diastolic "shock" may be felt in the pulmonary area due to forcible closure of the pulmonic valves. The pulmonic second sound is greatly accentuated and systolic and diastolic murmurs along the left border of the sternum are common. Gallop rhythm may be present. In terminal stages congestive right-sided heart failure may appear; more often death occurs before gross signs of failure develop.

Radiographically, the most characteristic finding is a prominent pulmonary artery segment on the left border of the heart (Figure 3). The vascular markings in the peripheral portion of the lungs will vary with the underlying cause: they may be normal, greatly increased as in atrial septal defects and in mitral stenosis, or greatly diminished as in primary pulmonary vascular sclerosis and essential pulmonary hypertension. The heart may or may not appear enlarged; in the stage of hypertrophy without dilatation the right ventricle often looks normal on the posteroanterior film. With pronounced right ventricular hypertrophy and clockwise rotation of the heart, the cardiac silhouette is often enlarged to the left and may be wrongly interpreted as left ventricular hypertrophy. In point of fact this leftward extension of the cardiac shadow is due to enlargement of the right ventricle; at autopsy the left ventricle may be found even smaller than normal.

The electrocardiogram offers important aid in the diagnosis of cor pulmonale. The most definitive evidence of right ventricular hypertrophy is reversal of the QRS pattern in the precordial leads. The right precordial leads (V_4R, V_3R, V_1, V_2) exhibit tall R-waves with relatively small S-waves and the left precordial leads (V_5, V_6) have small R-waves and relatively deep S-waves. The onset of the intrinsicoid deflection is delayed in the right precordial leads and accelerated in the left, averaging from .03 to .05 seconds in the former and .02 to .03 seconds in the latter—likewise a reversal of the normal relationship. The T-waves are usually inverted in V_1 to V_4 and upright in V_5 and V_6; occasionally they are inverted in all the precordial leads, probably a reflection of associated left ventricular disease.

Less definitive patterns associated with cor pulmonale are incomplete RBBB and less frequently complete RBBB. The latter is more often seen in primary left ventricular disease but occasionally is encountered as a complication of cor pulmonale.

The standard leads usually exhibit marked right axis deviation, a non-specific sign dependent upon the vertical position and clockwise rotation of the heart (Figure 2). However, since right axis deviation is the most constant single finding in the electrocardiogram of right ventricular hypertrophy, it must be regarded as an important component of the cor pulmonale pattern.

Tall, sharply-spiked P-waves (P-pulmonale) are often seen in standard leads II and III and in AVF, probably a reflection of right auricular hypertrophy or dilatation. Although not pathognomonic, this finding affords confirmatory evidence for the diagnosis of cor pulmonale.

Two points merit special emphasis: (1) the patterns associated with cor pulmonale are independent of etiology—similar or almost identical tracings may be obtained in atrial septal defect, in primary pulmonary vascular sclerosis or in mitral stenosis; (2) a completely normal tracing may be found in well-advanced cases of cor pulmonale; hence, the absence of electrocardiographic evidence of right ventricular hypertrophy does not exclude this lesion.

Treatment

Treatment is directed primarily toward the relief of the underlying cardio-pulmonary diseases and their complications. This implies early recognition and treatment of chronic broncho-pulmonary infection (obstructive emphysema, pneumonitis, bronchitis, bronciectasis, asthma)*, and the early surgical correction of reversible cardiac lesions and thoracic cage deformities. For essential pulmonary hypertension or primary pulmonary vascular disease (sclerotic or thrombo-embolic) little of lasting therapeutic value is available, since the underlying pathological process is essentially irreversible. Temporary favorable results have been reported from the use of ganglionic blocking agents (hexamethonium bromide)[17] and from adrenolytic drugs (Priscoline).[7] Some relief has also been reported from various surgical procedures such as sympathectomy and vagotomy. The rationale for these procedures is the assumption that a reversible increment of "spasm" is superimposed on the organic vascular obstruction.

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*For a comprehensive discussion of this phase of therapy and a detailed description of specific measures the reader is referred to a recent article by Simon Dack.[18]

Management of congestive failure affecting primarily the right ventricle does not differ essentially from the treatment of any other type of congestive heart failure. Digitalis, salt restriction, diuretics and regulation of activity are usually effective, albeit to a less marked degree; also the results achieved are apt to endure for a shorter period of time.

SUMMARY

Since the term cor pulmonale was first introduced a quarter century ago, it has come to mean different things to different people. A more rational approach to the semantology of the term is suggested. On this basis, cor pulmonale is defined as "right ventricular hypertrophy due to a disordered pulmonary circulation," regardless of the cause. "Pulmonary heart disease," "emphysema heart" and "pulmonary hypertensive heart disease," are types of cor pulmonale; each refers to right ventricular hypertrophy of more or less specific origin. Brief notes on diagnosis and treatment are presented.

RESUMEN

Desde que el término cor pulmonale se introdujo hace un cuarto de siglo, ha significado diferentes cosas a también diferentes personas. Una interpretación más racional del término se sugiere. Sobre esta base el cor pulmonale se defino como "hipertrofia ventricular derecha debida a trastornos de la circulación pulmonar" cualquiera que sea le causa. "Enfermedad cardiaca pulmonar," "Corazón enfisematoso" y "Enfermedad cardiaca hipertensiva pulmonar" son formas de cor pulmonale. Cada uno de estos términos se refiere a hipertrofia ventricular de origen más o menos específico. Se presentan resúmenes sobre diagnóstico y tratamiento.

RESUME

Depuis que le terme de "coeur pulmonaire" a été utilisé pour la première fois il y a un quart de siècle, il est arrivé à avoir des significations différentes selon les auteurs. I. C. Brill suggère qu'on revienne à une définition proche de la signification véritable de ce terme. Sur cette base, le coeur pulmonaire doit être défini comme "une hypertrophie ventriculaire droite, due à un trouble de la circulation pulmonaire," quelle qu'en soit la cause. Le coeur des affections pulmonaires, le coeur emphysémateux, et le coeur de l'hypertension pulmonaire sont des types de coeurs pulmo-

naires; chacun d'entre eux est dû à une hypertrophie ventriculaire droite d'origine plus ou moins spécifique. L'auteur présente de brèves conclusions sur le diagnostic et le traitement.

ZUSAMMENFASSUNG

Nachdem die Bezeichnung cor pulmonale erstmals von einem Vierteljahrhundert eingeführt worden ist, ist es mittlerweile dazu gekommen, dass jederman etwas anderes darunter versteht. Es wird eine mehr zweckmässige Einstellung auf die wirkliche Bedeutung der Bezeichnung vorgeschlagen. Auf dieser Basis wird das cor pulmonale definiert als "Hypertrophie des rechten Ventrikels infolge einer gestörten Lungencirculation" unbeschadet der Ursache. "Pulmonale Herzerkrankung," "Emphysemherz" und "pulmonale, mit Bluthahdruck einhergehende Herzerkrankung" sind Typen des cor pulmonale; jeder bezieht sich auf eine Hypertrophie des rechten Ventrikels mehr oder weniger spezifischen Ursprungs. Kurze Bemerkungen über Diagnose und Behandlung werden angeschlossen.

REFERENCES

1 White, P. D.: "Heart Disease," Ed. 1, New York, The Macmillan Co., 1931.

2 White, P. D.: "Heart Disease," Ed. 4, New York, The Macmillan Co., 1931.

3 Fishman, A. P. and Richards, D. W.: "The Management of Cor Pulmonale in Chronic Pulmonary Disease, With Particular Reference to the Associated Disturbances in the Pulmonary Circulation," *Am. Heart J.*, 52:149, 1956.

4 Griffith, G. C.: "Cor Pulmonale: Its Diagnosis and Management," *Dis. Chest*, 29: 258, 1956.

5 Oram, S.: "Chronic Cor Pulmonale," *The Practitioner*, 176:272, 1956.

6 Mack, I. and Snider, G. L.: "Respiratory Insufficiency and Chronic Cor Pulmonale," *Circulation*, 13:419, 1956.

7 Hecht, H. H.: "Heart Failure and Lung Disease," *Circulation*, 14:265, 1956.

8 Spatt, S. D. and Grayzel, D. W.: "Cor Pulmonale: Observations on Forty-Two Autopsied Patients," *Am. J. Med.*, 5:252, 1948.

9 Rubin, E. L.: "The Size of the Heart in Asthma and Emphysema," *Lancet*, 2:1089, 1936.

10 McKeown, F.: "The Pathology of Pulmonary Heart Disease," *Brit. Heart J.*, 14: 5, 1952.

11 White, P. D. and Brenner, O.: "Pathological and Clinical Aspects of the Pulmonary Circulation," *N.E. J. Med.*, 209:1261, 1933.

12 Gray, F. D., Jr.: "Kyphoscoliosis and Heart Disease," *J. Chronic Dis.*, 4:499, 1956.

13 Burroughs, R. W. and Sparkman, D. R.: "Diseases of the Pulmonary Circulation," *N. W. Med.*, 55:879, 1956.

14 Brill, I. C.: "The Clinical Manifestations of the Various Types of Right-Sided Heart Failure (Cor Pulmonale)," *Ann. Int. Med.*, 13:513, 1939.

15 Dexter, L., Lewis, B. M., Hayes, F. W., Gorlin, R. and Houssay, H. E. J.: "Chronic Cor Pulmonale Without Hypoxia," *Bull. New England Med. Center*, 14:69, 1952.

16 Barr, J. R. and Knox, Fred, H., Jr.: "Embolic Obstruction of Major Pulmonary Arteries Producing Chronic Cor Pulmonale," *Dis. Chest*, 29:225, 1956.

17 Davies, L. G., Goodwin, J. F. and Van Leuven, B. D.: "The Nature of Pulmonary Hypertension in Mitral Stenosis," *Brit. Heart J.*, 16:440, 1954.

18 Dack, S.: "The Present Status of the Treatment of Cor Pulmonale," *N. Y. State J. Med.*, 57:74, 1957.

The Treatment of Shock in Myocardial Infarction

Definition of Shock of Myocardial Infarction

In evaluating the effects of treatment on the natural prognosis of "shock" accompanying myocardial infarction, it is essential to define this type of circulatory failure irrespective of the possible misuse of the term "shock" in this context. The generally accepted clinical pattern in all types of shock consists of slightly cyanotic pallor, cold skin, excessive sweating, restlessness, weakness and tachycardia. These signs vary in occurrence and intensity. The apparent critical characteristic of the life-endangering shock of myocardial infarction is severe prolonged hypotension which may occur at the onset of the attack during the first day or from the second to the fourth day.

The reported fatality rates in untreated shock of myocardial infarction range from 60 to 90 per cent. The variation arises largely from the differences in criteria of "severity" and "duration." The two elements may operate independently or concomitantly in affecting prognosis. For instance, a blood pressure that falls to an unobtainable level will represent a threat to life if it persists for 15 minutes, or even less. A fall in systolic pressure to 85 mm. Hg. which lasts for four hours, if accompanied by such evidence of circulatory inadequacy as an hourly renal output of only 10 ml. of urine, is equally likely to lead to death. The pre-infarction blood pressure apparently influences the critical level of shock production. Thus, a hypertensive patient with fixed pressures of over 180/110 mm. Hg. may enter a shocklike state when his pressure falls to 110/70 mm. Hg., whereas a person whose "normal" pressure is 94/60 mm. Hg. may exhibit no apparent shock with a fall to 80/50 mm. Hg. Fixing an arbitrary critical level of blood pressure or duration of hypotension which is applicable in all cases is impossible. Accumulated experience and reports in the literature, however, indicate that in a normotensive patient a decrease in systolic blood pressure to below 85 mm. Hg. which persists for over one hour is generally accompanied by the other features of shock and, if not treated, denotes a poor prognosis. If the hypotension persists over three hours the shock becomes "irreversible," and 90 per cent of such cases terminate fatally irrespective of possible transient response to heroic therapy.

Approximately one-half of all patients exhibiting systolic hypotension of 60 to 80 mm. Hg. for ½ hour or less spontaneously recover without demonstrable ill effects. Hypotension with systolic blood pressure levels between 70 and 85 mm. Hg. may be maintained for 12 to 72 hours in certain patients who show no other manifestations of shock and who may excrete from 200 to 400 ml. of urine daily. However, over 80 per cent of these patients, if not treated, develop severe and fatal irreversible shock. Attempts at correcting the hypotension are strongly recommended in such cases.

Mechanisms of Shock

The current knowledge of the basic mechanism of the shock of myocardial infarction and irreversible shock dictates to some degree the therapy employed. Two elements leading to hypotension are recognized as being precipitated by myocardial infarction. The first consists of myocardial failure and reduced cardiac output.[1-3] The frequent occurrence of mild to severe pulmonary edema and of prolonged circulation rates, as well as ballooning of areas of heart muscle as observed by roentgenkymography, clinically corroborates this concept. In such cases administration of oxygen by nasal cannula, mask or tent seems warranted. Digitalis glycosides are widely recommended, but whereas no contraindication exists for their use in nontoxic doses, they appear to be of little or no immediate benefit except in atrial flutter or fibrillation. The second element leading to hypotension is a peripheral vascular reaction resulting in a) failure of maintenance of arterial resistance in the presence of lowered cardiac output,[4] and b) possible decrease of peripheral and visceral venous tone with maintenance of constriction of outlet visceral veins, resulting in venous pooling, as demonstrated experimentally in other forms of hypotension by Smith and Hoobler[5] and by Weil, et al.[6]

Pressor Drug Therapy

The use of pressor agents, which by acting on the arterial bed and possibly on the venous bed increase arterial resistance and improve the return of blood to the heart, has been the most successful method of treating the shock of infarction. The fear that these drugs, by causing arterial constriction, may further deprive tissues of blood has not been substantiated clinically, as evidenced by the significant increase in the rate of survival of patients treated for shock with these agents. Whereas a patient with normal coronary arterial circulation may survive hypotension, those with diffuse occlusive coronary arterial disease probably require an adequate "head" of arterial pressure to avoid either additional or extended and advancing myocardial deterioration and failure.

The commonly employed pressor agents with transient action are Paredrine (hydroxyamphetamine hydrobromide), Propadrine (phenylpropanolamine hydrochloride), Neo-Synephrine (phenylephrine hydrochloride), and Wyamine (mephentermine). In addition to their vasopressor effect, the latter two drugs have an inotropic (affecting the force of muscular contractions) myocardial action. They all should be administered by intramuscular or intravenous injection in doses of 5 mg. to 25 mg., although Wyamine has been safely used in doses of 50 mg. The duration of pressor response to these drugs rarely exceeds ½ hour. They may be repeated, but if the hypotension is severe or recurs after one to three doses, administration of long-acting pressor agents is advisable.

The most dramatic pressor effect is obtained by continuous intravenous drip infusion of *l*-norepinephrine.[7-9] The action takes place within 30 seconds and after withdrawal ceases within a similar period. Thus, precise titration of the drug to the patient at a rate of 10 to 30 drops a minute (0.5 to 1.5 ml.) is required. The flow is maintained at a rate under 1.5 ml. per minute (2.0 to 2.5 liters per day) to avoid flooding the patient. The infusion may be introduced through a cannula placed in the inferior vena cava via the femoral vein when long periods of infusion seem probable. The drug should be given in a concentration of 4 mg. per liter of 5 per cent glucose solution; it is inactivated if given in blood or plasma. If this concentration is ineffective, the amount may be increased to 8 mg. per liter and progressively to 60 mg. per liter. On one occasion infusion of 100 mg. per liter was necessary to successfully bridge a critical period. In general, however, if infusion of *l*-norepinephrine in a concentration greater than 24 mg. per liter for over an hour is ineffective, recovery is unlikely.

During therapy the patient must be constantly monitored by skilled attendants and ¼ to ½ hourly records of rate of flow and concentration of the drug, and blood pressure, pulse and respiration must be maintained. The cessation of the infusion is attempted only after gradual decrease of dosage, and a glucose drip is maintained for at least one hour after the drug is stopped. The reappearance of severe hypotension may quickly result in a resistant shock if the flow cannot be rapidly started.

l-norepinephrine has several undesirable effects. 1. It may cause slough of skin and deeper tissue after accidental extravasation of fluid. This may be counteracted by prompt multiple subcutaneous injections of 10 to 20 mg. of tolazoline hydrochloride (Priscoline) or of phentolamine hydrochloride (Regitine),[11] in 20 ml. of saline solution. 2. The transiency of the action of *l*-norepinephrine results in prompt hypotension if the infusion flow ceases abruptly. 3. The drug may lower total renal blood flow. This effect, however, has no significant influence on the favorable increase of urine secretion following restoration of adequate blood pressure. 4. The necessity of introducing 1.5 to 2.5 liters of intravenous solution may flood the patient. Flooding may be prevented by increasing the concentration of the drug in the infusion and by diminishing the rate of flow. Diuretics may be given concomitantly if fluid and sodium retention occurs, as is generally the case in shock or congestive failure and as is observed as a stress phenomenon in 75 per cent of cases of uncomplicated myocardial infarction.[12] 5. Focal hepatic necrosis has been found at autopsy in patients who received *l*-norepinephrine,[13] but no clinical evidence of hepatic insufficiency has been noted in surviving patients treated for shock with this drug.

Griffith[10] recommends adding 15 mg. of heparin to each 500 ml. of norepinephrine in 5 per cent glucose solution for intravenous drip infusion. The addition of heparin a) prevents thrombosis of the vein receiving the infusion, b) diminishes the severity of leakage sloughs, and c) possibly increases the chances of recovery from irreversible shock.

Metaraminol (Aramine)[14] possesses the same advantage as norepinephrine in raising the blood pressure by inotropic effect on both heart muscle and peripheral vascular pressor reactions. It may be administered intravenously as a drip infusion in a dose of 300 to 1000 mg. per liter of 5 per cent glucose or by intravenous injection of a single dose of 5 to 25 mg. It does not produce as rapid and as high an elevation of blood pressure as norepinephrine, and occasionally it fails to produce a pressor effect in cases where the latter drug may be successful. It has an advantage in that after the blood pressure has been raised to an effective level by drip infusion or by intravenous injection of a single dose, it may be administered subcutaneously in doses of 5 to 30 mg. at intervals of ½ to 2-½ hours. This route is feasible since Aramine generally retains its pressor effect for 30 to 120 minutes and since it does not cause tissue necrosis proportionate to its pressor effect. In addition, it probably causes less decrease of renal blood flow than norepinephrine.

The mechanism of restoration of natural pressor influences is not known. With therapy the resumption of normal pressure may be either abrupt or gradual. For this reason pressor agents may be required for periods of one hour to 20 days before recovery. Six hours to three days of treatment are not unusual.

Irreversible Shock

"Irreversible" shock is likely to develop if hypotension is not corrected within three hours. Recovery occurs in only about 10 per cent of such patients treated with pressor agents. The causes of irreversible shock are not known, but several reasons have been given for the failure of a patient to respond to treatment and for the transiency of pressor responses to drugs. These are a) the release of ferritin or vasodepressor substance (VDM) by the hypoxic liver, b) the development of acidosis which diminishes the effects of pressor amine drugs, and incidentally tends toward precipitation of cardiac arrhythmias,[15] c) decreased blood coagulability and formation of multiple thrombi in the lungs, brain and kidney,[16] d) absorption into the blood of rapidly developing bacterial exotoxin from the hypoxic intestinal tract,[17] e) further damage to the myocardium by ischemia and hypoxia as evidenced specifically by faulty carbohydrate metabolism of the muscle,[18] and f) possible adrenal secretory insufficiency. In the light of these possible causes, oxygen inhalation, administration of heparin and of adequate amounts of fluid and carbohydrate by parenteral or oral routes, use of intestinal antibiotics, e.g., Bacitracin or Polymyxin, and alkalinizing therapy without concomitant sodium retention may be considered theoretically valuable. Unfortunately, none of these measures has been clinically proved to increase the chances of a patient's recovery, although all have been effective in animal experimentation. In certain cases administration of adrenal corticoids, such as hydrocortisone, 100 to 300 mg. intravenously, has seemed to potentiate the action of the pressor amine drugs, as has been demonstrated experimentally[19-21]; generally, however, such therapy is ineffective.

Other measures used in the treatment of shock include: 1. Rapid transfusion or plasma infusion (except in patients with elevated venous pressure) by the intravenous route (3 to 10 ml. per minute)[22, 23] or by the intra-arterial route (10 to 50 ml. per minute).[24] 2. Hypothermia has been reported by Weil in shock of bacteremic infarction[25] and by Vogelsang in shock of myocardial infarction.[26] The latter author reported that three patients with severe hypotension promptly recovered after infusion of 250 ml. of iced (4° C.) plasma. No confirmation of these results has been reported. 3. General care of the patient is important, including adequate rest without excessive use of opiates which cause respiratory depression or antidiuretic effects, attention to bowels and skin, and oral intake of food. Any serious arrythmia should be corrected, but it should be noted that Pronestyl may accentuate the hypotension.

Conclusions

The hypotension complicating acute myocardial infarction presents a threat to life when it is manifested by a shocklike clinical pattern, especially if associated with severe oliguria. The critical level of hypotension is dependent on the pre-infarction blood pressure.

If the hypotension is very severe or persists over three hours the shock becomes irreversible and chances of successful therapy are greatly reduced. Definitive therapy should be instituted promptly and maintained until recovery is assured.

Transient benefits may be obtained by use of short-acting pressor amines and transfusions, but in general recovery is dependent on the use of the longer-acting pressor drugs, *l*-norepinephrine and metaraminol (Aramine). Constant monitoring of the patient's condition and of the therapy is necessary.

Since both myocardial failure[27] and peripheral vasomotor mechanisms are responsible for shock, additional measures are recommended, namely, oxygen inhalation, use of digitalis and heparin, adequate carbohydrate and fluid intake, and avoidance of sodium and water accumulation and acidosis. Adrenal corticoids may be helpful in potentiating the pressor amines, but clinically they have not proved consistently valuable.

REFERENCES

1 Gazes, P. C., Goldberg, L. I. and Darby, T. D.: "Heart Force Effects of Sympathomimetic Amines as a Basis for Their Use in Shock Accompanying Myocardial Infarction," *Circulation*, 8:883, 1953.

2 Sarnoff, S. J., Case, R. B., Berglund, E. and Sarnoff, L. C.: "Ventricular Function: V. The Circulatory Effects of Aramine; Mechanism of Action of Vasopressor Drugs in Cardiogenic Shock," *Circulation*, 10:84, 1954.

3 Gamill, J. F., [illegible] l, C. E., Fernald, J. D. and Atennucci, A. J.: "Hemodynamic [illegible] Acute Myocardial Infarction Using the Dye Injection Method for Cardiac Output Determination," *Ann. Int. Med.*, 43:100, 1955.

4 Agress, C. M., Glassner, H. F., Binder, M. J. and Fields, J.: "Hemodynamic Measurements in Experimental Coronary Shock, *J. Appl. Physiol.*, 10:469, 1957.

5 Smith, J. R. and Hoobler, S. W.: "Acute and Chronic Cardiovascular Effects of Pentolinium in Hypertensive Patients," *Circulation*, 14:1061, 1956.

6 Weil, M. H., Hinshaw, L. B., Visscher, M. B., Spink, W. W. and MacLean, L. D.: "Hemodynamic Effects of Vasopressor Agent (Metaraminol) and Hypotension in Dogs Produced by Endotoxin," *Proc. Soc. Exper. Biol. & Med.*, 92:610, 1956.

7 Goldenberg, M., Apgar, V., Deterling, R. A., Jr. and Pines, K. L.: "Norepinepherine (Arterenol, Sympathin N) as Pressor Drug," *J.A.M.A.*, 140:776, 1949.

8 Moyer, J. H., Skelton, J. M. and Mills, L. C.: "Nor-epinephrine: Effect in Normal Subjects; Use in Treatment of Shock Unresponsive to Other Measures," *Am. J. Med.*, 15:330, 1953.

9 Sampson, J. J. and Zipser, A.: "Norepinephrine in Shock Following Myocardial Infarction," *Circulation*, 9:38, 1954.

10 Sampson, J. J. and Griffith, G. C.: "Norepinephrine in the Treatment of the Elderly Patient," *Geriatrics*, 11:60, 1956.

11 Close, A. S. and Kory, R. C.: "Cutaneous Necrosis Due to Norepinephrine: Mechanism and Prevention," *Clin. Res. Proc.*, 4:241, 1956.

12 Sampson, J. J., Kalmansohn, R. B., Klinghoffer, K. A., Friedman, M. and Toch, P.: *Sodium and Chloride Retention Following Myocardial Infarction.* Communications, 1^{er} Congres Mondial de Cardiologie, J. B. Bailliere and Fils, Paris, 1952. Vol. 2, Pp. 448-453.

13 Brunson, J. G., Eckman, P. L. and Campbell, J. B.: "The Increasing Incidence of Unexplained Liver Necrosis," *U. Minn. Med. Bull.*, 28:197, 1957.

14 Moyer, J. H. and Beazley, H. L.: "Effectiveness of Aramine in the Treatment of Shock," *Am. Heart J.*, 50:136, 1955.

15 Houle, D. B., Weil, M. H., Brown, E. B., Jr. and Campbell, G. S.: "Influence of Respiratory Acidosis on ECG and Pressor Responses to Epinephrine, Norepinephrine, and Metaraminol," *Proc. Soc. Exper. Biol. & Med.*, 94:561, 1957.

16 Crowell, J. W. and Read, W. L.: "Hyperactivity of the Blood Coagulability Control Mechanism—A Possible Cause of Irreversible Shock," *Am. J. Med.*, 19:138, 1955.

17 Schweinburg, F. B., Shapiro, P. B., Frank, E. D. and Fine, J.: "Host Resistance in Hemorrhagic Shock. Demonstration of Circulating Lethal Toxin in Hemorrhagic Shock," *Proc. Soc. Exper. Biol. & Med.*, 95:646, 1957.

18 Hackel, D. B. and Goodale, W. T.: "Effects of Hemorrhagic Shock on the Heart and Circulation of Intact Dogs," *Circulation*, 11:628, 1955.

19 Kurtland, G. S. and Freedberg, A. S.: "The potentiating Effect of ACTH and of Cortisone on Pressor Response to Intravenous Infusion of L-Nor-Epinephrine," *Proc. Soc. Exper. Biol & Med.*, 78:28, 1951.

20 Ramey, E. R., Goldstein, M. S. and Levine, R.: "Action of Nor-epinephrine and Adrenal Cortical Steroids on Blood Pressure and Work Performance of Adrenalectomized dogs," *Am. J. Physiol.*, 165:450, 1951.

21 Fritz, I. and Levine, R.: "Action of Adrenal Cortical Steroids and Nor-epinephrine on Vascular Responses of Stress in Adrenalectomized Rats," *Am. J. Physiol.*, 165:456, 1951.

22 Sampson, J. J. and Singer, I. M.: "Plasma and Blood Infusion Following Myocardial Infarction," *Circulation*, 9:38, 1954.

23 Epstein, F. H. and Relman, A. S.: "Transfusion Treatment of Shock Due to Myocardial Infarction," *New England J. Med.*, 241:889, 1949.

24 Berman, E. F. and Akman, L. C.: "Intra-arterial Infusion in the Treatment of Shock Resulting from Coronary Occlusion," *Am. Heart J.*, 43:264, 1952.

25 Weil, M. H.: "Current Concepts on Management of Shock," *Circulation*, 16:1097, 1957.

26 Vogelsang, A.: "Rapid Cold Plasma Infusion Treatment for Severe Shock (Peripheral Failure) Following Coronary Occlusion," *Canadian Med. J.*, 77:232, 1957.

27 Sampson, J. J., Felton, L. R., Goetz, A. A., Solomon, B. and Axelrad, B.: "Portable Serial Roentgenkymography in Acute Myocardial Infarction," *Circulation*, 13:729, 1956.

JOHN J. SAMPSON, M.D., F.C.C.P.*
San Francisco, California

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*From the Department of Medicine, University of California School of Medicine, and Mount Zion Hospital.

THE ELECTROCARDIOGRAM OF THE MONTH

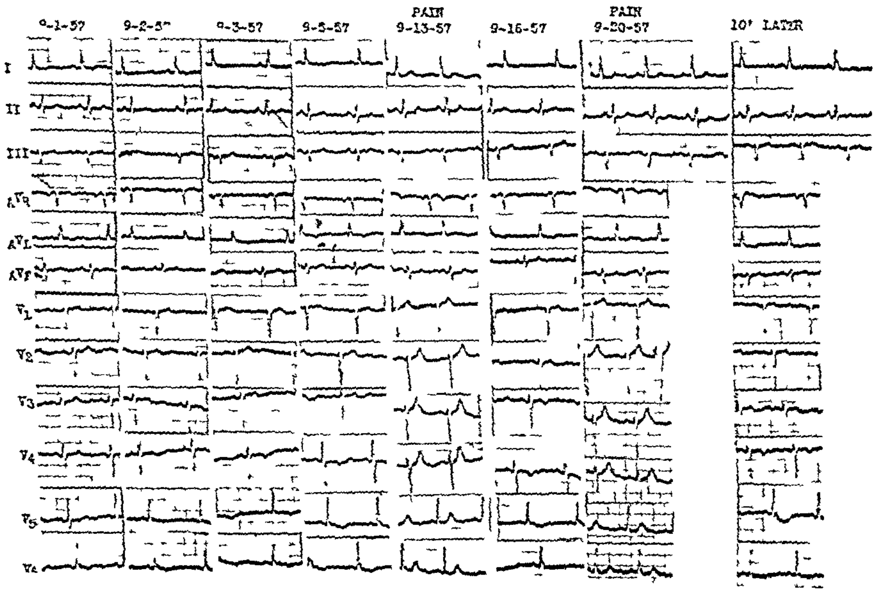
The authors would be pleased to receive comment and controversy from readers in relation to explanations offered.

A 70-year-old white woman had had intermittent discomfort in the epigastrium and lower anterior chest for several months. Attributing these to indigestion she ignored them until September 1, 1957, when a more persistent attack occurred. The electrocardiogram made on the date of admission to the hospital (September 1, 1957) and several others (September 2, 3, and 5) showed changes in the T waves. It was noted that the recurrences of discomfort that occurred in the hospital followed meals. In the mind of her physician this raised the suspicion of gall bladder disease or diaphragmatic hernia. However, it was suggested that an electrocardiogram be made *during the discomfort.* This was accomplished twice (September 13 and 20, 1957).

It is noted that previously inverted T waves became upright during each attack. As a matter of fact, the electrocardiogram of September 13 has a normal appearance except for the inverted U waves in Leads I, V_4, V_5, V_6. It is interesting to note that the U waves are upright in the same leads when discomfort is absent. Nitroglycerine invariably relieved the discomfort within three minutes.

It is important to point out that had the first electrocardiogram been made during discomfort, the one on September 13 might have been interpreted as normal (except for the inverted U waves). Accordingly, when an electrocardiographic investigation of discomfort in the chest is being carried out it is wise to record a second tracing after administering nitroglycerine. A change in the tracing following nitroglycerine such as that which occurred on September 20 is of the greatest diagnostic significance, even if no discomfort is present just prior to or during the observations.

MANUEL GARDBERG, M.D., and IRVING L. ROSEN, M.D.*
New Orleans, Louisiana



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*Cardiac Research Laboratory, Touro Infirmary and the Department of Medicine, Louisiana State University Medical School

Editorial

The Value and Significance of International Congresses

In responding to the Editor's request for an article on the value of international medical congresses, I recall an analogy I made in discussing this subject at the Third International Congress of our College at Barcelona.

Flying up the length of the African continent with the leisurely gait of a flying boat to attend our first congress in Rome, we passed over the great African lakes, the source of the river Nile, and then over the vast Sudd region, one of the world's unique natural phenomena. For several hours, and covering hundreds of miles, we flew over a vast plain thinly covered with water so that stunted shrubs on tiny hillocks barely raised themselves above the flat mirror which continuously reflected the disc of the sun. It was this vast spongy marsh, called the Sudd, which baulked the efforts of the early geographers in tracing the Nile to its source. As we approached Khartoum we could see the river taking definite shape until, reinforced by the waters of the Blue Nile from the Abyssinian highlands, it became the mighty stream which has played so unique a part in history, as it still does in the vital economy of the land of Egypt. Carrying with it the rich silt of the African hinterland, the Nile, depositing this wealth in its lower reaches, becomes the very life-blood of Egypt; and this feature alone has made possible a civilization which has stretched back over fifty centuries.

Musing on these matters, it seemed to me to present an analogy of the manner in which we at times foregather from all quarters of the earth into a strong body with a designed scientific outlook. Meeting together thus, and pooling our knowledge, our experiences, and our discoveries, we give direction and force to the most vital of the sciences in the life of mankind. Here we crystallize ideas into vital concepts and in the fire of debate mould them into weapons against disease and death.

To many participants the stimulating atmosphere of the scientific exchanges is of the utmost value, to others again it connotes the shedding of certain shibboleths, the abandonment of methods which have been shown to be false fads. To those whose minds still retain a measure of youthful elasticity, in short, those who can accept and accommodate new ideas, such a conference can be a fine regenerating experience.

So much, very briefly, for the primary function of a great medical congress; this, at least, is the goal at which every carefully designed congress is aimed. We may not always achieve a demonstrable scientific result, but there are other effects, perhaps even more important, which are always attained in a greater or lesser degree.

The spirit of camaraderie, of brotherly helpfulness, that pervades the conference goes a long way to cement the basic friendliness of man to man, breaking down barriers of caste, of nation, and of race. United in a common bond of knowledge of the healing art, dedicated in common to the alleviation of human suffering, we cannot fail to perceive that the service of Humanity is a thing above and apart from political and national boundaries.

The proof of this is demonstrated almost daily. Let there befall some great catastrophe, be it fire, or famine or pestilence; and we hasten to extend our help in a truly Hippocratic spirit right across political frontiers, because we are dealing with suffering fellow human-beings.

Such then is the pure humanitarian spirit which still has to find room in the hearts of our political-dictators before any conference on World Peace can be successful.

Gathered together in our great congresses, bound by the age-old dicta of Hippocrates, let us do our utmost to foster this spirit while worshipping at the altar of scientific knowledge. So doing we must inevitably spread the leavening influence of this broad humanitarianism until it breaks down the barriers and 'curtains' which still becloud our horizon.

DAVID P. MARAIS, M.D., F.C.C.P.*
Capetown, South Africa

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*Chairman, Council on African and Eastern Affairs.

FIFTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

Tokyo, Japan September 7-11, 1958

Judging from advance registration and the interest expressed by physicians throughout the world, it appears that the Congress to be held in Tokyo, Japan, September 7-11, 1958, will be highly successful. The Congress is sponsored by the Council on International Affairs of the American College of Chest Physicians and presented under the patronage of the Government of Japan and the Japan Science Council, with the Honorable Nobusuke Kishi, Prime Minister of Japan, serving as the Honorary President. The Congress has been endorsed by the Japan Medical Association. The following scientific and social program will be presented.

SCIENTIFIC PROGRAM

Monday, September 8, 1958

Morning Session, Hall I—Tuberculosis

Chairmen:

Taizo Kumagai, Professor of Internal Medicine and Phthisiology, Research Institute for Tuberculosis and Leprosy, Sendai, Japan

Donald R. McKay, Associate Clinical Professor of Medicine, University of Buffalo School of Medicine, Buffalo, New York, U.S.A.

Kanamycin

Hamao Umezawa, Tokyo, Japan

The Natural History of Tuberculosis in the Human Body

J. Arthur Myers, Professor of Internal Medicine and Public Health, Medical and Graduate Schools, University of Minnesota, Minneapolis, Minnesota, U.S.A.

Blood Concentrations of INH in Systemic Pulmonary Suprahepatic and Porta Vessels

Ovidio Garcia-Rosell, Professor of Phthisiology, University of San Marcos, Lima, Peru

In Vitro and In Vivo Activities of Kanamycin

Ken Yanagisawa, Tokyo, Japan

Tuberculin Skin Sensitivity in Old Age

O. D. Beresford, Poole Chest Clinic, Dorset, England

Diabetes and Tuberculosis: Clinical Aspects

Andrew L. Banyai, Professor of Medicine, Emeritus, Marquette University School of Medicine, Milwaukee, Wisconsin, U.S.A.

Clinical Experience in Tuberculosis

Paul Santy, Professor of Clinical Surgery, Hopital E. Herriot, Lyon, France

PANEL DISCUSSION ON TUBERCULOSIS

Moderator:

Hastings H. Walker, Medical Director, Leahi Hospital, Honolulu, Hawaii

Panel:

Miguel D. Canizares, Medical Director, Quezon Institute, Quezon City, Philippines

Imasato Donomae, Professor of Internal Medicine, Osaka University, Osaka, Japan

Peter W. Edwards, Honorary Consulting Chest Physician, Birmingham Regional Hospital Board, Market Drayton, England

Celal Ertug, Professor of Chest and Tuberculosis Service, School of Medicine, Ankara University, Ankara, Turkey

Morning Session, Hall II—Miscellaneous Topics

Chairmen:

Arao Imamura, Emeritus Professor of Medicine, Faculty of Medicine, Osaka University, Osaka, Japan

Raman Viswanathan, Director, Patel Chest Institute, University of Delhi, Delhi, India

Treatment of Hydatid Cyst of the Lung

Basile P. Karageorgis, Chief Surgeon, State Hospital, Athens, Greece

Pulmonary Eosinophilosis

John R. Wilson, Lecturer in Chest Diseases, University of Ceylon, Colombo, Ceylon

A Therapy of Tuberculosis by Intravenous, Intracavitary and Intrafistular Instillation of Fat and Fatty Acid Colloid

Yoneji Miyagawa, Professor of Medicine, Tokyo University, Tokyo, Japan

The Use of a Reversed Gastric Tube to Replace the Esophagus

Henry J. Heimlich, Assistant Clinical Professor of Surgery, New York Medical College, New York, New York, U.S.A.

Dyspnee et Systeme Nerveux Role Diencephalique Troubles Foncionnels
André Dussert, Meynard Public Sanatorium, Bergerac, France

The Significance and Possible Causes of Non-Specific Tuberculin Sensitivity
Lydia B. Edwards, Medical Director, Tuberculosis Program, Division of Special Health Services, Department of Health, Education and Welfare, Washington, D. C., U.S.A.

Experimental Anastomosis of the Pulmonary Artery to the Right Auricle
N. Salonikides, M. Frangopoulos and Constantin J. Tountas, Assistant Professor of Surgery, University of Athens Medical School, Athens, Greece

Experimental and Clinical Experience with a Valvular Prosthesis in the Correction of Interatrial and Interventricular Septal Defects
Ramon Larios, Medical Director, Sanatorio Nacional, Tegucigalpa, Honduras, Edward Fitch, Gumersindo Blanco and Charles P. Bailey, Bailey Thoracic Clinic, Philadelphia, Pennsylvania, U.S.A.

The Treatment of Pulmonary Tuberculosis from Standpoint of Surgery
Masao Tsuzuki, Medical Director, Japanese Red Cross Hospital, Tokyo, Japan

Results of Aortic Homografts Preserved in 80% Alcohol and 4% Formalin. Experimental Study
Giocondo Villanova Artigas, Sanatorio do Fortao-Curitiba, Curitiba, Brazil

Present Day Aspects of Cardiovascular Physiologic Problems in Aviation Medicine
H. A. Smedal, Captain, MC, United States Navy

Afternoon Session, Hall I—A - Fungus Infections
B - Clinical Aspects of Cardiopulmonary Function Studies

Chairmen:
Attilio Omodei Zorini, Director, Carlo Forlanini Institute, Rome, Italy
Andrew L. Banyai, Professor of Medicine, Emeritus, Marquette University School of Medicine, Milwaukee, Wisconsin, U.S.A.

Symposium on Fungus Infections

Modern Laboratory Methods in the Diagnosis of Systemic Fungus Infection, Including Tissue Cultures
Howard Larsh, Department of Health, Education and Welfare, Public Health Service, Kansas City, Kansas, U.S.A.

Clinical Recognition and Treatment of Histoplasmosis and Blastomycosis
Michael L. Furcolow, Medical Director, Chief, Kansas City Field Station, Department of Health, Education and Welfare, Public Health Service, Kansas City, Kansas, U.S.A.

Medical and Surgical Treatment of Coccidioidomycosis
William A. Winn, Medical Director, Tulare-Kings Counties Sanatorium, Springville, California, U.S.A.

The Clinical Aspects of Cardiopulmonary Function Studies

Disability Evaluation Following Chest Injury
Friedrich W. Koch, Städtische Krankenanstalten, Essen, Germany

Pulmonary Insufficiency Among Japanese People
Jiro Ishida, Medical Director of Tuberculose Clinic and Hiroshi Sasamoto, Associate Professor of Medicine, Keio University, Tokyo, Japan

Principles of Ventilatory Control in Pulmonary Emphysema; Priority of Diminution of Breathing Energy over the Respiratory Center
Alvan L. Barach, Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, U.S.A.

Cardiorespiratory Function in Thoracic Surgery
Miyoshi Urabe, Professor of Surgery, University of Kanazawa Medical School, Kanazawa, Japan

Comparison of Results of Pneumoangiographical Examinations with Those Obtained Through Isotope Thoracography in Lung Diseases
Wilhelm Bolt and Hans Rink, University of Cologne, Cologne, Germany

PANEL DISCUSSION ON CARDIOPULMONARY FUNCTION

Moderator:
Noboru Kimura, Kyushu University Medical School, Fukuoka, Japan

Panel:
Alvan L. Barach, Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, U.S.A.
Alfonso de la Fuente, Professor of Surgery, Faculty of Medicine, University of Madrid, Madrid, Spain
Hugo W. Knipping, Medical Director, University Clinic, University of Cologne, Cologne, Germany
Raul F. Vaccarezza, Professor of Tuberculosis, University of Buenos Aires, Buenos Aires, Argentina

Afternoon Session, Hall II—Miscellaneous Topics

Chairmen:

Miguel D. Canizares, Director, Quezon Institute, Quezon City, Philippines
Ovidio Garcia-Rosell, Professor of Phthisiology, University of San Marcos, Lima, Peru

Etiology and Surgical Treatment of Pigeon Chest
Henry A. Brodkin, Chief Medical Director, New Jersey Department of Labor and Industry, Newark, New Jersey, U.S.A.

Enzyme Therapy in the Triad: Paranasal Sinus Disease, Allergic Asthmatic Bronchitis, and Bronchiectasis
Nathan E. Silbert, Chief of Allergy, Lawrence Quigley Hospital, Lynn, Massachusetts, U.S.A.

The Pharmacological Study of Tubercle Bacillus
Pyung Suh Yu, Professor of Internal Medicine, Soodo Medical College, Seoul, Korea

Post-Bronchographic Protein-Bound Iodine Levels
Somchai Bovornkitti, Sunthorn Tandhanand and Panpit Pantasuwan, Siriraj Hospital Medical School, Dhonburi, Thailand

The Cellular Structures of Tubercle Bacilli
Tadao Toda, Kenji Takeya and Massatsu Koike, Tuberculosis Institute, Kyushu University Medical School, Fukuoka, Japan

Treatment of Tuberculous Cervical Lynphadenitis
Mumtaz Hussain, Lahore, Pakistan

Effects of Isoniazid on Plasma Lipids
Lyle A. Baker, Associate Clinical Professor of Medicine, University of Illinois College of Medicine, John E. Berry and Jonas Salna, Chicago, Illinois, U.S.A.

Early Ambulation in the Treatment of Spontaneous Pneumothorax
Fred N. Miller, Director, Student Health Service, University of Oregon, Eugene, Oregon, U.S.A.

Detailed Electronmicroscopic Studies on Purified Bacterial and Viral DNA with Consideration of Their Relation to Genetics
Masanaka Terada, Professor of Bacteriology, The Tokyo Jikeikai School of Medicine, Tokyo, Japan

Treatment of Hydatid Cyst of the Lung
Yudhveer Sachdeva, Professor of Clinical Surgery, Medical College, Amritsar, India

Ten Years' Experience with Routine Chest X-Rays in a General Hospital
Walter E. Kunstler, Associate Surgeon, Royal Edward Laurentian Hospital, Montreal, P.Q., Canada

The Mitochondrial Structure of Mycobacterium Tuberculosis Relating to its Function
Toshiaki Ebina, Medical Director, Research Institute for Tuberculosis and Leprosy, Tohoku University, and Chikatomo Shinohara, Sendai, Japan

Hydatid Cysts of the Mediastinum
P. Guedj, Constantine, Algeria

Pathologisch Veranderte Lungenvenen Im Hilus
Alfred Stecken, Medizinischen Klinik der Charite, Berlin, Germany

The Philadelphia Pulmonary Neoplasm Research Project
David A. Cooper, Professor of Medicine, University of Pennsylvania School of Medicine, and Katharine R. Boucot, Professor of Preventive Medicine, Woman's Medical College, Philadelphia, Pennsylvania, U.S.A.

Clinical and Roentgenological Courses of Pulmonary Paragonomiasis
Sze-Piao Yang, Professor of Internal Medicine, and Chin-Tang Huang and Lan-Chang Chiang, National Taiwan University Hospital, Taipei, Taiwan

Tuesday, September 9, 1958

Morning Session, Hall I—The Heart and Circulation

Chairmen:

Burgess L. Gordon, Director of Education, Lovelace Foundation, Albuquerque, New Mexico, U.S.A.
Hugo W. Knipping, Medical Director, University Clinic, University of Cologne, Cologne, Germany

A Clinico-Pathological Analysis of Cardiopulmonary Death Among 300 Autopsied Cases
Shigeo Okinaka and Hiomi Homma, University of Tokyo Medical School, Tokyo, Japan

Postthrombotic Syndrome
Mario Degni, Chief Surgeon, Casa de Saude Matarozzo, Sao Paulo, Brazil

A Preliminary Survey on Coronary Disease; Medical Research in East Pakistan
Mohammad Ibrahim, Professor of Clinical Medicine, Medical College Hospital, Dacca, Pakistan

The Diagnosis of Coronary Artery Disease
Edward C. Rosenow, Jr., Associate Clinical Professor of Medicine, University of Southern California School of Medicine, Pasadena, California, U.S.A.

Open Cardiac Surgery
Yoshio Ozawa, Professor of Medicine, Osaka University Hospital, Osaka, Japan

Principal Determinants of Coronary Flow
Lauro B. de Vera, Professorial Lecturer in Cardiac Surgery and Cardiophysiology, University of The East, Manila, Philippines, Eliot Corday, Herbert Gold, and John Williams, University of California School of Medicine, Los Angeles, California, U.S.A.

The Value of Continuous Postural Drainage in the Relief and Elimination of Chronic Cough
L. Bedford Elwell, Honorary Consultant Physician, Mater Misericordia Public Hospital, Brisbane, Australia

PANEL DISCUSSION ON CORONARY DISEASE

Moderator:
John F. Briggs, Associate Professor of Clinical Medicine, University of Minnesota Medical School, St. Paul, Minnesota, U.S.A.

Panel:
Tachio Kobayashi, Tokyo, Japan
Hans Rink, Director, Landeskrankenhaus Marienheide, Marienheide, Germany
David H. Waterman, Thoracic Surgeon, University of Tennessee Memorial Research Center and Hospital, Knoxville, Tennessee, U.S.A.

Morning Session, Hall II—Emphysema and Miscellaneous Topics

Chairmen:
Erik C. J. Hedvall, Professor of Phthisiology, University of Uppsala, Uppsala, Sweden
Seymour M. Farber, Associate Clinical Professor of Medicine, University of California School of Medicine, San Francisco, California, U.S.A.

Plastic Pencil Cap as a Problem of Bronchial Foreign Bodies
Jo Ono, Professor of Bronchoesophagology, Keio University Medical School, Tokyo, Japan

The Clinical Diagnosis and Classification of Mediastinal Masses
Harold A. Lyons, Associate Professor of Medicine, State University of New York Medical School, Brooklyn, Captain George L. Calvy, MC and Lieutenant Billy P. Sammons, MC, United States Navy, St. Albans, New York, U.S.A.

Physiologic Criteria for Surgery in Pulmonary Emphysema
Roger H. L. Wilson, Assistant Clinical Professor of Medicine, Orville F. Grimes and Michihiro Miyanishi, University of California School of Medicine, San Francisco, California, U.S.A.

Lung Abscess
Kingo Shinoi, Director, Department of Surgery, Tokyo Medical College Hospital, Tokyo, Japan

Pulmonary Manifestations of Leprosy
Jean Chenebault, Chief Physician, Centre de Pneumophthisiologie Hopital Colombani, Casablanca, Morocco

Segmental Resection in Pulmonary Tuberculosis
Yoshihiko F. Fujikawa, Thoracic Surgeon, Long Beach General Hospital, Long Beach, California, U.S.A.

Maintenance of Bronchial Drainage in Emphysema
S. Thatcher Hubbard, Jr., Director, Private Cardiorespiratory Function Laboratory, Spokane, Washington, U.S.A.

Amphotericin B in the Treatment of Deep Fungus Infections Including Coccidioidomycosis, Candidiasis, Cryptococcosis, Aspergillosis and Mycetoma
Thomas H. Sternberg, Professor of Medicine, Victor D. Newcomer, Edwin T. Wright and Ronald M. Reisner, University of California Medical Center, Los Angeles, California, U.S.A.

Sarcoidosis in Puerto Rico
Hector A. Martinez-Villafane, Clinical Associate in Medicine, University of Puerto Rico, San Juan, Puerto Rico

Appearance and Behavior of the Sputum in Water. Significance of the Rate of Sinking
Prasert Kangsadal, Professor of Medicine, Siriraj Hospital Medical School, Dhonburi, Sunthorn Tandhanand and Banyat Prijyanonda, Bangkok, Thailand

The High Incidence of Peptic Ulcer in Obstructive Emphysema with Cor Pulmonale
Mack L. Gottlieb, Chief Medical Officer, United States Veterans Administration Regional Office, Manila, Philippines

The Management of Cardiospasm
David H. Waterman, Thoracic Surgeon, University of Tennessee Memorial Research Center and Hospital, Knoxville, Tennessee, U.S.A.

Staphylococcal Pneumonia; Its Treatment and Complications
William C. Rountree, Major, MC and Manard E. Pont, Captain, MC, United States Air Force

Afternoon Session, Hall I—Benign and Malignant Tumors of the Chest

Chairmen:

Yoneji Miyagawa, Professor of Surgery, University of Tokyo College of Medicine, Tokyo, Japan

Raul F. Vaccarezza, Director, Tuberculosis Clinic and Professor of Pathology, Faculty of Medicine, University of Buenos Aires, Buenos Aires, Argentina

The Cytology of Lung Cancer in Heavy Smokers
Carlo Sirtori, Director and Professor, Istituto Nazionale per lo Studio e la Cura dei Tumori, Divisione di Anatomia e Istologia Patologica, Milan, Italy

Cancer of the Lung
Kunio Ota, Tokyo, Japan

The Incidence of Pulmonary Neoplasms in the World
Giovanni L'Eltore, Assistant Director, Carlo Forlanini Institute, Rome, Italy

Considerations of a Pathologist about the Cytodiagnosis of Bronchial Tumors, 500 Cases
Bernard Pierson, Chief of Research, Pathologic Anatomy, University of Nancy, Nancy, France

Cancer of the Lung
Kingo Shinoi, Professor of Medicine, Tokyo Medical College, and Shichiro Ishikawa, Assistant Professor of Medicine, Keio University Medical School Hospital, Tokyo, Japan

Pulmonary Cytology in Malignant and Nonmalignant Chest Diseases
Seymour M. Farber, In Charge, University of California Tuberculosis and Chest Service, San Francisco Hospital, Samuel L. Pharr and Ikuma Nagasawa, San Francisco, California, U.S.A.

The Importance of Pleural Biopsy for Research, Diagnosis and Therapy
Anton Sattler, Professor of Medicine, University of Vienna, Vienna, Austria

PANEL DISCUSSION ON BENIGN AND MALIGNANT TUMORS OF THE CHEST

Moderator:

Donato G. Alarcon, Professor of Clinical Medicine, National University of Mexico, Mexico City, Mexico

Panel:

Jean M. Dubois de Montreynaud, Pneumologist, Centre Reginal Anti-Cancereux, Reims, France

Chevalier L. Jackson, Professor of Laryngology and Bronchoesophagology, Temple University Medical Center, Philadelphia, Pennsylvania

Helge B. Wulff, Professor of Surgery, Lund University, Malmo, Sweden

Hisao Yamashita, Tokyo, Japan

Afternoon Session, Hall II—Cardiopulmonary Disease and Pediatrics

Chairmen:

M. R. Heynsius van den Berg, President, Royal Netherland-Central Association for the Prevention of Tuberculosis, Amsterdam, The Netherlands

Giovanni L'Eltore, Assistant Director, Carlo Forlanini Institute, Rome, Italy

Critical Conditions for Pneumonectomy and Their Management
Shichiro Ishikawa, Assistant Professor of Medicine, Keio University Medical School Hospital, Tokyo, Japan

Surgical Correction of Transposition of the Great Vessels
Thomas G. Baffes, Department of Surgery, Northwestern University Medical School, Chicago, Illinois, U.S.A.

The Diagnosis and Treatment of Arteriovenous Coronary Aneurysms in Infants and Children
Benjamin M. Gasul, Director, Pediatric Cardiophysiology Department, Cook County Children's Hospital, Chicago, Illinois, U.S.A.

Thirty-Three Year Review of Rheumatic Fever and Rheumatic Heart Disease in Rhode Island (1925-1958)
Banice Feinberg, Physician in Chief, Department of Pediatrics, Rhode Island Hospital, Providence, Rhode Island, U.S.A.

Cardiovalvuloscopy
Shigeru Sakakibara, Professor of Surgery, Heart Institute, Woman's Medical College, Tokyo, Japan

Lung Ventilation in Mitral Stenosis
Nicholas Tsamboulas, Professor of Medicine, E. Economides and G. Hadji Dimitriou, University of Athens, Athens, Greece

Isoniazid Therapy of Primary Tuberculosis in Children
Katherine H. K. Hsu, Assistant Professor of Pediatrics, Baylor University School of Medicine, Houston, Texas, U.S.A.

Therapeutic Pneumoperitoneum in Tuberculous Filipino Children
Mita Pardo de Tavera, Resident Physician, and Gloria Calderon, Quezon Institute, Quezon City, Philippines

Results from Current Trials of the Prophylactic Possibilities of Isoniazid in Preventing Meningitis and Other Complications of Primary Tuberculosis in Children
Frank Mount, Operational Research Section, Public Health Service Tuberculosis Program, Washington, D.C., U.S.A.

Immunization Against Tuberculosis with a Synthetic Antigen
Alberto P. Leon, Professor of Infectious Diseases, National University School of Medicine, Mexico City, Mexico

Myxoedema Heart In Children
I. P. Bronstein, Professor of Pediatrics, University of Illinois College of Medicine, Chicago, Illinois, U.S.A.

Wednesday, September 10, 1958

Morning Session, Hall I—Cardiovascular and Pulmonary Surgery

Chairmen:

Peter W. Edwards, Honorary Consulting Physician, Birmingham Regional Hospital Board, Market Drayton, England

J. E. J. Harris, Director, Student Health, University of New Mexico, Albuquerque, New Mexico, U.S.A.

Open Cardiac Surgery
Seiji Kimoto, Professor of Surgery, Tokyo University Hospital, and Shigeru Sakakibara, Tokyo, Japan

Funnel Plastic: A Treatment for Chronic Empyema Cavity
Karl Vossschulte, Professor of Surgery, University of Giessen, Giessen, Germany

Intracardiac Surgery Under Hypothermia and Extracorporeal Circulation
Helge B. Wulff, Professor of Surgery, Lund University, Malmo, Sweden

Demography of Cancer of the Lung
Donato G. Alarcon, Professor of Clinical Medicine, National University of Mexico, Mexico City, Mexico

Gosta-Pleuropneumonectomy
Nunzio M. DiPaola, Professor of Surgery, University of Rome, Rome, Italy

PANEL DISCUSSION ON AVIATION MEDICINE

Moderator:

Burgess L. Gordon, Director of Education, Lovelace Foundation, Albuquerque, New Mexico, U.S.A.

Panel:

James M. Davis, Lt. Col., MC, Director, Professional Services, Pacific Air Forces, United States Air Force

M. Frederick Leeds, Pan American World Airways, San Francisco, California, U.S.A.

Masamitsu Oshima, Tokyo, Japan

A. S. R. Peffers, Senior Medical Officer, British Overseas Airways Corporation, London, England

H. A. Smedal, Captain, MC, United States Navy

Morning Session, Hall II—Occupational Diseases of the Chest

Chairmen:

Paul Santy, Professor of Clinical Surgery, Hopital E. Herriot, Lyon, France

Anton Sattler, Professor of Medicine, University of Vienna, Vienna, Austria

Silicosis
Takashi Nakamura, Professor of Medicine, Tohoku University, Sendai, Japan

Certain Etiologic, Pathogenic and Clinical Aspects of Pneumonoconiosis
Raul F. Vaccarezza, Professor of Phthisiology, University of Buenos Aires, Buenos Aires, Argentina

Manganese Intoxication
Ubaldo Roldan V., Professor of Medicine, National University of Mexico, Mexico City, Mexico

Studies on Asbestosis
Zenji Horai, Professor of Medicine, Nara Medical College, Osaka, Japan

Silicosis
C. J. B. Muller, Head, Department of Radiology, Karl Bremer Hospital and University of Stellenbosch Medical Faculty, Cape Town, South Africa

Follow Up Studies of Simple Silicosis Among Retired Miners
Shuei Nozaki, Niigata, Japan

A Review of Beryliosis Therapy
Harry E. Tebrock, Assistant Professor of Research Pharmacology, University of Miami School of Medicine, Douglaston, New York, U.S.A.

Serum Isoniazid Concentrations in Japanese Females and the Effect of the Simultaneous Administration of PAS
W. C. Morse, Major, MC, T. S. Rei, F. T. Roque, Lt. Col., MC., and C. S. Christianson, Lt. Col., MC, United States Army, Camp Zama, Japan

Rheumatoid Pneumoconiosis
Jethro Gough, Professor of Pathology, Welsh National School of Medicine, Cardiff, Wales

Koniomycoses from Occupational Vegetable Powder Inhalation
Balazs Bugyi, Budapest, Hungary

Surgical Management of Acute Respiratory Emergencies
Henry J. Stanford, Thoracic Surgeon, Tucson Medical Center, Tucson, Arizona

Afternoon Session, Hall I—Bronchoesophagology and Miscellaneous Topics

Chairmen:

Donato G. Alarcon, Professor of Clinical Medicine, National University of Mexico, Mexico City, Mexico

Jo Ono, Professor of Bronchoesophagology, Keio University Medical School, Tokyo, Japan

The Historical Review of Chest Surgery in Japan
Hiroshige Shiota, President, Nippon Medical College, Tokyo, Japan

Vascular Anomalies Obstructing the Trachea and Esophagus; Their Diagnosis and Treatment
Paul H. Holinger, Professor of Bronchoesophagology, University of Illinois College of Medicine, Kenneth C. Johnston, William E. Riker and Willis J. Potts, Chicago, Illinois, U.S.A.

An Analysis of Five Year Survival Cases Following Radical Esophagectomy for Esophageal Cancer
Komei Nakayama, Professor of Surgery, Chiba University School of Medicine, Chiba City, Japan

Reconstruction of the Esophagus
Kwang-Shun Lu, Professor of Thoracic Surgery, National Defense Medical Center, Taipei, Taiwan

The Endoscopic Therapy of Parenchymal Tuberculosis
Albert A. Carabelli, Chief of Thoracic Medicine, St. Francis Hospital, Trenton, New Jersey, U.S.A.

Surgical Indications in Cancer of the Lung
Ettore Ruggieri, Director of Surgical Clinic, University of Naples, Naples, Italy

Cancer of the Esophagus
Luji Katsura, Sendai, Japan

Fifteen Unrecognized or Neglected Physical Signs in the Diagnosis of Chest Diseases
Coleman B. Rabin, Assistant Clinical Professor of Medicine, Columbia University, New York, New York, U.S.A.

The Study of Mycosis on a National Wide Scale Program Developed in Venezuela by the National Coordinating Commission
Jose Ignacio Baldo, Professor of Phthisiology, Central University School of Medicine, Caracas, Venezuela

The Pathology and Pathogenesis of Histoplasmosis
Henry C. Sweany, Director of Research, Pathology and Allied Sciences, Missouri State Sanatorium, Mount Vernon, Missouri, U.S.A.

A New Method of Treatment of Emphysema by Tracheal Fenestration
Edgar Mayer, Clinical Professor of Medicine, New York University Post Graduate Medical Center, Israel Rappaport and E. E. Rockey, New York, New York

Afternoon Session, Hall II—Miscellaneous Topics

Chairmen:

Eung Soo Han, Assistant Professor of Internal Medicine and Bacteriology, Taegu Medical College, Seoul, Korea

Hastings H. Walker, Medical Director, Leahi Hospital, Honolulu, Hawaii

The Relationship Between the Structure of the Pulmonary Lymph System and the Genesis and Development of Pulmonary Diseases
Chuzo Nagaishi, Professor of Surgery, Kyoto University, Kyoto, Japan

Ten Year Follow-Up of Antimicrobial Treatment of Pulmonary Tuberculosis
Hyman I. Sapoznik, Attending Physician, Chest Department, Michael Reese Hospital and David B. Radner, Chicago, Illinois, U.S.A.

Spontaneous Pneumothorax in Hawaii
Edmund L. Lee, Queen's Hospital, Honolulu, Hawaii

The Pathogenesis of Tuberculosis and the Prevention of Cavity Formation
Yuichi Yamamura, Professor of Biochemistry, Kyushu University Medical School, Toyonaka, Japan

Spontaneous Pneumothorax
Ralph Volk, Captain, MC, United States Navy, Yokosuka, Japan

Antituberculosis Program for El Salvador
Jose F. Valiente, Professor of Tisiology, University of El Salvador Medical School, San Salvador, El Salvador

Congenital Bronchoesophageal Fistula Without Esophageal Atresia
Bomy R. Billimoria, Honorary Thoracic Surgeon, St. George's and Masina Hospitals, Bombay, India

The Role of Humoral Factors in Native and Acquired Resistance to Tuberculosis
Shuusuke Tsuji, Professor of Medicine, Kyoto University, Kyoto, Japan

The Results of the Ambulant Chemo-Antibiotic Therapy from the Central Dispensary in Stockholm
Isador L. Bluhm, Docent Professor, Karoline Institute, Stockholm, Sweden

Laryngo-Tracheal-Bronchial Local Anesthesia by Nebulization
Aldo G. Remorino, Bronchoscopist, Hospital de los Ninos, Buenos Aires, Argentina

Die Contusio Thoracis und ihre Folgen
Helmut P. Kuemmerle, Universitats-Frauen-Klinik, Tuebingen, Germany

Surgical Treatment of Tuberculous Bronchostenosis and Hilar Lymphatic Tuberculosis
Yujiro Dotai, Keio University College of Medicine, Kanagawa, Japan

Present Status of Tuberculosis in Ceylon
George E. Ranawake, Chief of Tuberculosis, Ceylon Medical Department, Colombo, Ceylon

Pulmonary Manifestations of Some Tropical Diseases in Thailand
Ninat Chinachoti, Central Chest Clinic, and Banyat Prijyanonda, Bangkok, Thailand

The Problem of Non-Specific Stimuli in the Treatment of Pulmonary Tuberculosis
Lucjan A. Dobrowolski, Pulmonary Disease Hospital, Warsaw, Poland

Historical and Modern Advances in Cardiac Surgery
Elmer C. Rigby, Chief Consultant, Thoracic Surgery, State of California, Los Angeles, California, U.S.A.

Thursday, September 11, 1958

Morning Session, Hall I—Tuberculosis

Chairmen:

Jose Ignacio Baldo, Professor of Phthisiology, Central University of Venezuela, Caracas, Venezuela

Manuel Quisumbing, San Pablo City Hospital, San Pablo, Philippines

Control of Tuberculosis in Iran
Mohamad Yazdi, Director, Sanatorium Niavaran, Tehran, Iran

Cicatricial and Open Healing of Tuberculous Pulmonary Cavities and Its Impediments
Taizo Kumagai, Tohoku University, Sendai, Japan

Present Developments of Isoniazid Chemotherapy Against Tuberculosis in the Fields of Experimental, Human and Bovine Disease Protection
Attilio Omodei Zorini, Director, Carlo Forlanini Institute, Rome, Italy

Resection and Thoracoplasty
Paul Kyrle, Department of Surgery, University of Vienna, Vienna, Austria

A Strain Directly Producing Dihydrostreptomycin
Mitsuo Hori and Arao Imamura, Osaka University, Osaka, Japan

Treatment of Pulmonary Tuberculosis with Thiosemicarbazone-Isonicotil Hydrazide
Miguel Jimenez Sanchez, Professor of Clinical Medicine, Anti-Tuberculosis Sanatorium, Huipulco, Mexico

Scalene Node Biopsy (Daniels' Operation) in the Diagnosis of Diseases of the Chest
Erik J. Hedvall, Professor of Phthisiology, Uppsala University, Uppsala, Sweden

Tuberculosis in Industry
P. K. Ghosh, Associate Professor of Medicine, R. G. Kar Medical College Hospitals, Calcutta, India

Atypical Acid Fast Bacilli and Their Clinical Significance
Emil Bogen, Pathologist, and Ann D. Staatz, Head Physician, Olive View Sanatorium, Olive View, California, U.S.A.

The Value of Chemotherapy for Active Pulmonary Tuberculosis Patients Treated on an Out-Patient Basis in Korea
Eung Soo Han, Assistant Professor of Internal Medicine and Bacteriology, Taegu Medical College of Korea, Kiho Kim and Hae Won Pyun, Seoul, Korea

Morning Session, Hall II—Miscellaneous Topics

Chairmen:

Pholpoke Thip, Instructor in Surgery, Army Medical Service School, Bangkok, Thailand

M. Jay Flipse, Jackson Memorial Hospital, Miami, Florida, U.S.A.

Tumors of the Thymus Gland
Seizo Katsunuma, President, Nagoya University, Nagoya, Japan

Differential Diagnosis and Therapy of the Pulmonary Manifestations of Collagen Diseases
Dieter Koch-Weser, Associate Professor of Medicine, Western Reserve University School of Medicine, and Antonio Carlos Debes, Cleveland, Ohio, U.S.A.

Pulmonary Acariasis
Manabu Sasa, Tokyo, Japan

The Detection of M. Tuberculosis in Sputum by the Use of X-Irradiated Guinea Pigs
Joseph A. Schwartz, Assistant Professor of Medicine, University of California Medical School, Charles M. Carpenter and A. W. C. Naylor-Foote, Los Angeles, California, U.S.A.

Pulmonary Paragonimiasis in Japan
Ichiro Miyazaki, Fukuoka, Japan

Gastrointestinal Manifestations in Posterior Wall Myocardial Infarction
A. David Etess, Attending Physician, Loomis Hospital, Liberty, New York

Surgical Casectomy
Yasuyuki Kano, Professor of Surgery, Keio University, Tokyo, Japan

Vocal Cord Paralysis Related to Diseases of the Neck and Thorax
Nathaniel M. Levin, Clinical Assistant Professor of Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Bronchiectasis and Cystic Diseases of the Lung
Naoshi Kumagai and Shogo Awataguchi, Tohoku University, Sendai, Japan

Radiological Evaluation of the Heart Size in Relation to Surface Area and Shape of Chest in Normal Individuals
Samuel A. Weisman, Clinical Associate Professor of Medicine, University of Southern California, Norman Zheutlin and Bernard J. O'Loughlin, University of California, Los Angeles, California, U.S.A.

Steroid Therapy and Tuberculosis
Harry Shubin, President of Staff and Chief, Department of Pulmonary Diseases, Philadelphia General Hospital, Philadelphia, Pennsylvania, U.S.A.

Roentgenologic Problems in Chest Diseases
Hans Martin Landecker, Honorary Chest Physician, Chest Clinic, Anti-tuberculosis Association, Sydney, Australia

A Simple Method for Evaluating a New Oral Bronchodilator
Richard I. H. Wang, Indianapolis General Hospital and Robert E. Shipley, Indianapolis, Indiana, U.S.A.

Pulmonary Bilharziasis
Taha M. Gomaa, Assistant Professor of Medicine, Cairo University, Cairo, Egypt

The Treatment of Various Forms of Primary Infections with Cortico-Steroids
Joaquin Escobar Perez, Assistant Professor of Medical Pathology, San Carlos University, Guatemala City, Guatemala

Coincident Pulmonary Tuberculosis and Respiratory Symptoms from Extrinsic Allergy
Ruth W. Wilson, Clinic Chief, State Tuberculosis Clinic, Rochester, Pennsylvania

The Problem of Tuberculosis in East Pakistan
Mohammed Giasuddin, Dacca, East Pakistan

FIRESIDE CONFERENCES

Subjects and Discussion Leaders

Thursday afternoon, September 11

Management of Emphysema

Andrew L. Banyai, Professor of Medicine, Emeritus, Marquette University School of Medicine, Milwaukee, Wisconsin, U.S.A.
Alvan L. Barach, Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, U.S.A.
Donald R. McKay, Associate Clinical Professor of Medicine, University of Buffalo School of Medicine, Buffalo, New York, U.S.A.
Makoto Murao, Chief, Internal Medicine, Tokyo University Hospital Policlinic, Tokyo, Japan
Tetsuro Yokoyama, Assistant, Department of Medicine, Cardiopulmonary Laboratory, Keio University, Tokyo, Japan

Cardiac Physiology: Vectorcardiography: Ballistocardiography

Eiichi Kimura, Sendai, Japan
Noboru Kimura, Kyushu University Medical School, Fukuoka, Japan
E. A. McMaster, Internist, Seaforth Medical Clinic, Seaforth, Ontario, Canada
Yasushi Mizuno, Nagoya University Hospital, Nagoya, Japan
Shiro Osajima, Professor of Internal Medicine, [illegible]
Gerhard Schumacher, Chief of Internal [illegible] Hospital, Berlin, Germany

Treatment of Pulmonary Infections, Medical and Surgical

Seymour M. Farber, Associate Clinical Professor of Medicine, University of California School of Medicine, San Francisco, California, U.S.A.
Sukehiro Higuchi, Professor of Radiology, Jikeikai Medical School, Tokyo, Japan
Jacob L. Marks, Fox River Tuberculosis Sanitarium, Chicago, Illinois, U.S.A.
Howard F. Root, Lecturer in Medicine, Harvard Medical School, Boston, Massachusetts, U.S.A.

Surgery, Chemotherapy and Radiation Therapy of Lung Tumors

Donato G. Alarcon, Professor of Clinical Medicine, University of Mexico, Mexico City, Mexico
Fortunato S. Guerrero, Professor of Surgery, University of Santo Tomas, Pasay City, Philippines
Kiyoshi Inada, Instructor in Surgery, Okayama University Medical School, Okayama, Japan
Juan S. Netto, Asuncion, Paraguay
Henry J. Stanford, Thoracic Surgeon, Tucson Medical Center, Tucson, Arizona
Kempo Tsukamoto, Tokyo, Japan

Bronchoesophagology

Arthur G. Falls, President, Medical Staff and Senior Attending Surgeon, Provident Hospital, Chicago, Illinois, U.S.A.
Joseph E. Ferkany, Kula Sanatorium, Waiakoa, Maui, Hawaii
Paul H. Holinger, Professor of Bronchoesophagology, University of Illinois College of Medicine, Chicago, Illinois, U.S.A.
Chevalier L. Jackson, Professor of Laryngology and Bronchoesophagology, Temple University School of Medicine, Philadelphia, Pennsylvania, U.S.A.
Jo Ono, Professor of Bronchoesophagology, Keio University Medical School, Tokyo, Japan
M. A. Pollock, Pollock Clinic, Toronto, Ontario, Canada
Philip Strax, Director of Radiology, Elmhurst General Hospital, New York, U.S.A.
Kaoru Yamamoto, Professor of Bronchoesophagology, Osaka Municipal University Medical School, Osaka, Japan

Management of the Coronary Patient

John F. Briggs, Associate Clinical Professor of Medicine, University of Minnesota Medical School, St. Paul, Minnesota, U.S.A.
Kenzo Oshima, Professor of Internal Medicine, Nihon University Medical College, Tokyo, Japan
Nicholas Tsamboulas, Professor of Medicine, University of Athens, Athens, Greece

Congestive Heart Failure

Joseph F. Borg, Assistant Clinical Professor of Medicine, University of Minnesota Medical School, St. Paul, Minnesota, U.S.A.
Harvey L. Daiell, Director, Scientific Department, Lakeside Laboratories, Milwaukee, Wisconsin, U.S.A.
Albert L. Maisel, President, Bernalilli County Indian Hospital, Albuquerque, New Mexico, U.S.A.
Yanosuke Sagawa, Kyoto, Japan
Junichi Wakisaka, Kurume, Japan

Surgery of the Coronary Artery and Others

Bomy R. Billimoria, Honorary Thoracic Surgeon, St. George's and Masina Hospitals, Bombay, India
Franklin R. Smith, Clinical Associate, Department of Surgery, University of Washington School of Medicine, Seattle, Washington, U.S.A.
Arthur E. Strauss, Assistant Clinical Professor of Clinical Medicine, Emeritus, Washington University Medical School, St. Louis, Missouri, U.S.A.
Saburo Sugie, Tokyo, Japan

Fungus Infections

Orin J. Farness, Tucson Medical Center, Tucson, Arizona, U.S.A.
Ladislao Pollak, Chief, Diagnosis Section, Department of Bacteriology, Instituto Nacional de Tuberculosis, Caracas, Venezuela
Henry C. Sweany, Director of Research, Pathology and Allied Sciences, Missouri State Sanatorium, Mt. Vernon, Missouri, U.S.A.

Chemotherapy of Tuberculosis

Manuel Albertal, Director, Sanatorio Albertal, Buenos Aires, Argentina
Shinnosuke Fujita, Chief, Tuberculosis Division, Tokyo Communications Hospital, Tokyo, Japan
Yoshimitsu Fukuhara, Department of Clinical Research, Institute for Infectious Diseases, University of Tokyo Medical School, Tokyo, Japan
Jiro Gomi, Assistant Professor of Medicine, Keio University School of Medicine, Tokyo, Japan
Fumio Ito, Doonomae Medical Clinic, Osaka University Hospital, Osaka, Japan
Yuzo Kawamori, Professor of Medicine, Kumamoto University School of Medicine, Kumamoto, Japan
Osamu Kitamoto, Professor of Medicine, University of Tokyo Medical School, Tokyo, Japan
Miklos Lanyi, Assistant Professor and Chief, Laboratory Service, University Medical School, Budapest, Hungary
Jiro Mikami, Chief, Department of Pulmonary Disease, First Tokyo National Hospital, Tokyo, Japan
Masukazu Naito, Associate Professor, Tuberculosis Institute, Kyoto University, Kyoto, Japan
Charles K. Petter, Superintendent and Medical Director, Lake County Tuberculosis Sanatorium, Waukegan, Illinois, U.S.A.
David B. Rosenthal, Director of Tuberculosis, Department of Health, Melbourne, Australia
Shigeichi Sunahara, Director, Tokyo National Sanatorium, Tokyo, Japan
Kin Yamada, Chief, Department of Internal Medicine, Tokyo Jikeikai School of Medicine, Tokyo, Japan
A. Omodei Zorini, Director, Carlo Forlanini Institute, Rome, Italy

Surgery of Heart Valves

Seiji Kimoto, Chief, Department of Surgery, Tokyo University Hospital, Tokyo, Japan
Yoshio Ozawa, Professor of Medicine, Osaka University Hospital, Osaka, Japan
Shigeru Sakakibara, Professor of Cardiovascular Surgery, Tokyo Women's Medical College, Tokyo, Japan
Rudolph T. Wagner, Adjunct Professor of Medicine, University of Miami School of Medicine, Miami Beach, Florida, U.S.A.
Helge B. Wulff, Professor of Surgery, Lund University, Malmo, Sweden

Asthma

Takayoshi Misawa, Tokyo, Japan
Philip H. Narodick, Clinical Instructor, University of Washington School of Medicine, Seattle, Washington, U.S.A.
Nathan E. Silbert, Chief of Allergy, Lawrence Quigley Memorial Hospital and Soldier's Home, Lynn, Massachusetts, U.S.A.
Hitohiko Sugiwara, Tokyo, Japan
Masuichi Takino, Dai Nippin Zoki Institute for Medical Research, Osaka, Japan

BCG Vaccination and Chemoprophylaxis

Yasuyuki Chiba, Medical Director, Health Control Department, National Railway and Tokyo Hospital, Tokyo, Japan
Erik J. Hedvall, Professor of Phthisiology, Uppsala University, Uppsala, Sweden
Katsumi Kaida, Professor and Chief, Research Institutes, Kyushu University Faculty of Medicine, Tukuoka, Japan
Iwao Kanno, Assistant Professor, Research Institute for Tuberculosis, Tohoku University, Sendai, Japan
Manuel Quisumbing, Sr., Visiting Physician, San Pablo City Hospital, San Pablo City, Philippines
S. Sen, First Physician, Tata Main Hospital, Jamshedpur, India
J. C. T'ao, Medical Director, Provincial Taipei Tuberculosis Control Center, Taipei, Taiwan